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WO 2004/069823 A1

(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions.

INHIBITORS OF HISTONE DEACETYLASE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Application 10/358,556.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity.

Summary of the Related Art

[0003] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0004] Csordas, *Biochem. J.*, **286**: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the αεε-amino groups of *N*-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science,* **272**: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al*. further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0005] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**: 4868-4873 (1999), teaches that HDACs is divided into two classes, the first represented by yeast Rpd3-like proteins, and the second

represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the second class of HDACs. Kao *et al.*, *Genes & Dev.*, **14**: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. Van den Wyngaert, *FEBS*, **478**: 77-83 (2000) discloses HDAC8, a new member of the first class of HDACs.

[0006] Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, **95**: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, *Exper. Cell Res.*, **177**: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G_1 and G_2 phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin *et al.*, *Nature*, **401**: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki *et al.*, U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme et *al.*, WO 01/38322 and PCT IB01/00683, disclose additional compounds that serve as HDAC inhibitors.

[0007] The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**:4868-4873 (1999), teaches that HDACs may be divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC-1, HDAC-2, and HDAC-3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC-4, HDAC-5, and HDAC-6, which are members of the second class of HDACs. Kao *et al.*, *Gene & Development* **14**:55-66 (2000), discloses an additional member of this second class, called HDAC-7. More recently, Hu, E. *et al.* J. Bio. Chem. **275**:15254-13264 (2000) discloses the newest member of the first class of histone deacetylases, HDAC-8. It has been unclear what roles these individual HDAC enzymes play.

[0008] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the

treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art. There is thus a need to identify additional HDAC inhibitors and to identify the structural features required for potent HDAC inhibitory activity.

BRIEF SUMMARY OF THE INVENTION

[0009] The invention provides compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0010] In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

[0011] In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

[0012] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

[0013] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 is a graph showing the antitumor activity of compound **106** in an HCT 116 human colorectal tumor model.

[0015] Figures 2-11 show additional data for other compounds used in the *in vivo* experiment described in Assay Example 2.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0017] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0018] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the αεε-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0019] The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

[0020] Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0021] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural

circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.* CH_3-CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-. Also, a number of moieties disclosed herein exist in multiple tautomeric forms, all of which are intended to be encompassed by any given tautomeric structure.

[0022] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A "C_0" hydrocarbyl is used to refer to a covalent bond. Thus, "C_0-C_3-hydrocarbyl" includes a covalent bond, methyl, ethyl, propyl, and cyclopropyl.

[0023] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A "C_0" alkyl (as in "C_0-C_3-alkyl") is a covalent bond (like "C_0" hydrocarbyl).

[0024] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0025] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0026] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0027] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0028] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteratom selected from the group consisting of O, S, and N.

[0029] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is $(C_1$-$C_6)$alk$(C_6$-$C_{10})$aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0030] A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. The heterocyclic

group is optionally substituted on carbon at one or more positions. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocyles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0031] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroalkyl groups comprise a C_1-C_6 alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0032] An "arylene," "heteroarylene," or "heterocyclylene" group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0033] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl,

chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0034] As employed herein, when a moiety (*e.g.*, cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

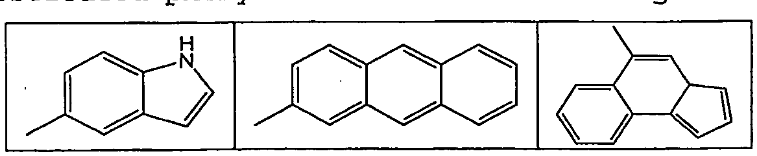
(a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

(b) C_1-C_5 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8 alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 *N*-alkyl carbamoyl, C_2-C_{15} *N,N*-dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

(c) $-(CH_2)_s-NR^{30}R^{31}$, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R^{30} and R^{31} are each independently hydrogen, cyano, oxo, carboxamido, amidino, C_1-C_8 hydroxyalkyl, C_1-C_3 alkylaryl, aryl-C_1-C_3 alkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, aryl-C_1-C_3 alkoxycarbonyl, C_2-C_8 acyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

R^{30} and R^{31} taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0035] In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 10-12 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. For example, an optionally substituted phenyl includes the following:



[0036] A "halohydrocarbyl" is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

[0037] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH_2-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH_2, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0038] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

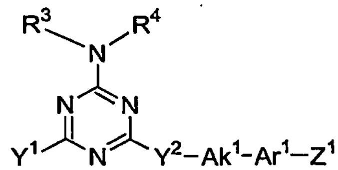
[0039] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl -CO-).

[0040] An "unsubstituted" moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0041] Preferred embodiments of a particular genus of compounds of the invention include combinations of preferred embodiments. For example, paragraph [0043] identifies a preferred Ay^1 and paragraph [0047] identifies preferred Ar^1 (both for compound (1) of paragraph [0042]). Thus, another preferred embodiment includes those compounds of formula (1) in paragraph [0042] in which Ay^1 is as defined in paragraph [0043] and Ar^1 is as defined in paragraph [0047].

Compounds

[0042] In a first aspect, the invention provides novel inhibitors of histone deacetylase. In a first embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):



(1)

and pharmaceutically acceptable salts thereof, wherein

R^3 and R^4 are independently selected from the group consisting of hydrogen, L^1, Cy^1, and $-L^1-Cy^1$, wherein

L^1 is C_1-C_6 alkyl, C_2-C_6 heteroalkyl, or C_3-C_6 alkenyl; and

Cy^1 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

R^3 and R^4 are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally forms part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

Y^1 is selected from the group consisting of $-N(R^1)(R^2)$, $-CH_2-C(O)-N(R^1)(R^2)$, halogen, and hydrogen, wherein

R^1 and R^2 are independently selected from the group consisting of hydrogen, L^1, Cy^1, and $-L^1-Cy^1$, wherein

L^1 is C_1-C_6 alkyl, C_2-C_6 heteroalkyl, or C_3-C_6 alkenyl; and

Cy^1 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

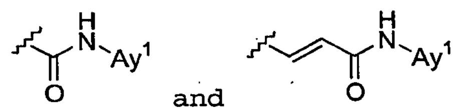
R^1 and R^2 are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally may form part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

Y^2 is a chemical bond or $N(R^0)$, where R^0 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl;

Ak^1 is C_1-C_6 alkylene, C_1-C_6-heteroalkylene (preferably, in which one $-CH_2-$ is replaced with -NH-, and more preferably $-NH-CH_2-$), C_2-C_6 alkenylene or C_2-C_6 alkynylene;

Ar^1 is arylene or heteroarylene, either of which optionally is substituted; and

Z^1 is selected from the group consisting of



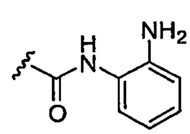
wherein Ay^1 is aryl or heteroaryl, which optionally is substituted.

[0043] Preferably in the compounds according to paragraph [0042], Ay^1 is phenyl or thienyl, each substituted with -OH or $-NH_2$.

[0044] More preferably in the compounds according to paragraph [0042], Ay^1 is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay^2 is attached.

[0045] More preferably in the compounds according to paragraph [0042], Ay^1 is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

[0046] In some preferred embodiments of the compounds according to paragraph [0042], Z^1 is



[0047] In some preferred embodiments of the compounds according to paragraph [0042], Ar^1 is phenylene. In some embodiments, Ak^1 is

alkylene, preferably methylene. In some preferred embodiments, Y^2 is -NH-. In some preferred embodiments, Y^1 is $-N(R^1)(R^2)$ or $-CH_2-C(O)-N(R^1)(R^2)$.

[0048] In some embodiments of the compounds according to paragraph [0042], R^1 and R^2 are each independently selected from the group consisting of hydrogen, L^1, Cy^1, and $-L^1-Cy^1$. In some embodiments, R^1 and/or R^2 is hydrogen. In other embodiments, R^1 and/or R^2 is alkyl or alkenyl, preferably allyl. In still other embodiments, R^1 and/or R^2 is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings. Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R^1 and/or R^2 is cycloalkyl, *e.g.*, cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

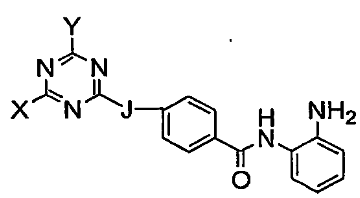
[0049] In some embodiments of the compounds according to paragraph [0042], R^3 and R^4 are each independently selected from the group consisting of hydrogen, L^1, Cy^1, and $-L^1-Cy^1$. In some embodiments, R^3 and/or R^4 is hydrogen. In other embodiments, R^3 and/or R^4 is alkyl or alkenyl, preferably allyl. In still other embodiments, R^3 and/or R^4 is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings. Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R^3 and/or R^4 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

[0050] As set forth above, L^1 is C_1-C_6 alkyl, C_2-C_6 heteroalkyl, or C_3-C_6 alkenyl. However, one skilled in the art will understand that when L^1 is not a terminal group, then L^1 is C_1-C_6 alkylene, C_2-C_6 heteroalkylene, or C_3-C_6 alkenylene. In some embodiments, L^1 is alkylene, preferably methylene or ethylene. In other embodiments, L^1 is alkenyl, preferably allyl. In some embodiments, Cy^1 is the radical of a heterocyclic group including, without limitation, piperidine, pyrrolidine, piperazine, and morpholine, each of which optionally is substituted and optionally is fused to one or more aryl rings. In other embodiments Cy^1 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl. In still other embodiments, Cy^1 is aryl or heteroaryl,

e.g., phenyl, pyridyl, or pyrrolyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy^1 is fused to one or two benzene rings. In some embodiments, Cy^1 has between one and about five substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo. Examples of preferred substituents include methyl, methoxy, and fluoro.

[0051] In some embodiments of the compounds according to paragraph [0042], R^1 and R^2 and/or R^3 and R^4 are taken together with the adjacent nitrogen atom to form a 5- or 6-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, and N, and wherein the ring optionally is substituted, and optionally is fused to one or more aryl rings. In some preferred embodiments, R^1 and R^2 and/or R^3 and R^4 are taken together with the adjacent nitrogen atom to form a ring such as, for example, pyrrolidine, piperidine, piperazine, and morpholine, wherein the ring optionally is substituted, and optionally is fused to an aryl ring. In some embodiments, the ring comprising R^1 and R^2 or R^3 and R^4 is fused to a benzene ring. In some embodiments, the ring comprising R^1 and R^2 or R^3 and R^4 has a substituent comprising an aryl or cycloalkyl ring, either of which optionally is substituted and optionally is fused to a cycloalkyl, aryl, heteroaryl, or heterocyclic ring. Preferred substituents include, without limitation, phenyl, phenylmethyl, and phenylethyl, the phenyl ring of which optionally is fused to a cycloalkyl, aryl, or heterocyclic ring.

[0052] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of formula 1(a):



(1a)

and pharmaceutically acceptable salts thereof, wherein

J is C_1-C_3-hydrocarbyl, $-N(R^{20})-$, $-N(R^{20})-CH_2-$, $-O-$, or $-O-CH_2-$;

R^{20} is -H or -Me;

X and Y are independently selected from $-NH_2$, cycloalkyl, heterocyclyl, aryl, heteroaryl, and A-$(C_1$-C_6-alkyl$)_n$-B-;

A is H, C_1-C_6-alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

B is -NH-, -O-, or a direct bond; and

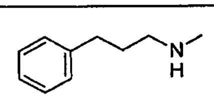
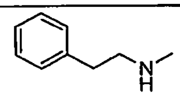
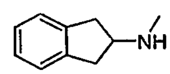
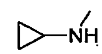
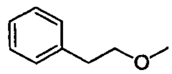
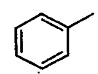
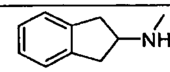
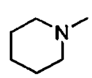
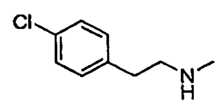
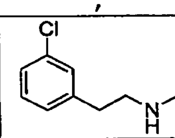
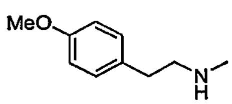
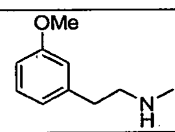
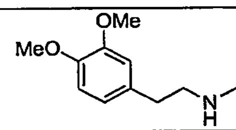
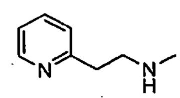
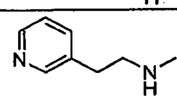
n is 0 (in which case A is directly bonded to B) or 1.

[0053] Preferably in the compounds according to paragraph [0052], A is phenyl optionally substituted with one or more moieties selected from halo (preferably chloro) and methoxy, and B is -NH-. In another preferred embodiment, A is selected from cyclopropyl, pyridinyl, and indanyl.

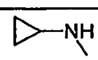
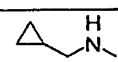
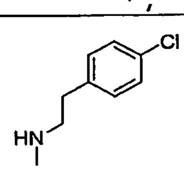
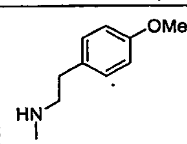
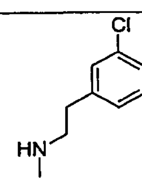
[0054] Preferably in the compounds according to paragraph [0052], J is -NH-CH_2-, -O-CH_2-, -N(CH_3)-CH_2-, -CH=CH-, or -CH_2-CH_2-.

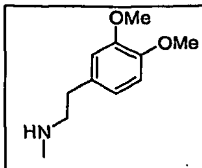
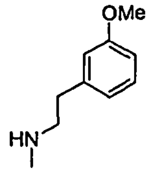
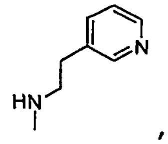
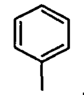
[0055] Preferably in the compounds according to paragraph [0052], R^{20} is -H.

[0056] In the compounds according to paragraph [0052] X is preferably selected from

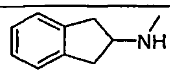
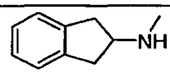
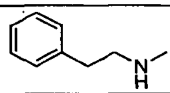
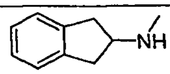
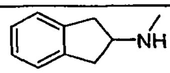
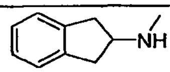
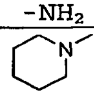
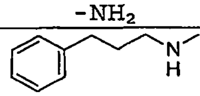
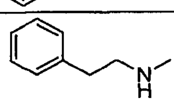
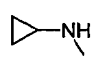
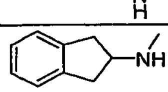
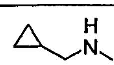
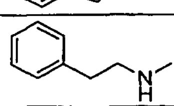
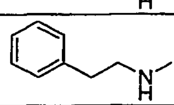
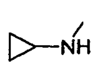
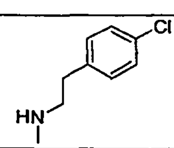
 ,	 ,	 ,	 ,
 ,	 ,	-OMe,	 ,
	-NH_2		
			
and	 ;		

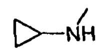
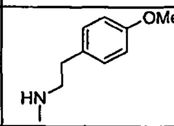
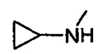
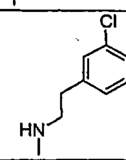
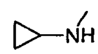
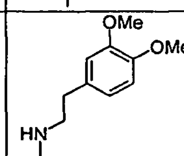
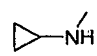
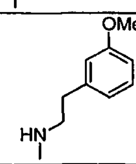
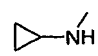
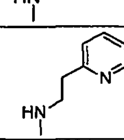
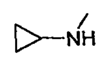
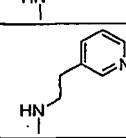
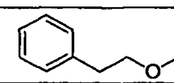
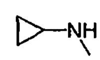
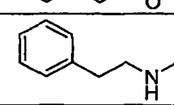
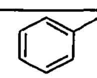
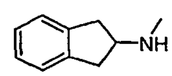
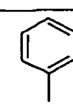
and Y is preferably selected from

-NH_2,	 ,	 ,	n-BuNH,
$MeOCH_2CH_2NH$,	 ,	 ,	 ,

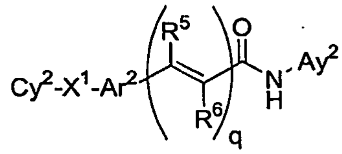
,	,	,	,
-H	Me	-OMe	$CH_3(CH_2)_3NH$-
and	$CH_3O(CH_2)_2$-NH-.		

[0057] In a more preferred embodiment of the compounds according to paragraph [0052], the HDAC inhibitors of the invention comprise the following compounds of formula 1a:

Cpd	J	X	Y
204	-NH-		$-NH_2$
207	$-OCH_2-$		$-NH_2$
210	$-NHCH_2-$		-H
212	$-NHCH_2-$	-OMe	-OMe
214	$-NHCH_2-$		-OMe
216	$-N(CH_3)-CH_2-$		-Me
218	$-NHCH_2-$		-Me
220	-CH=CH-	$-NH_2$	$-NH_2-$
223	-CH=CH-		$-NH_2$
224	$-CH_2CH_2-$	$-NH_2$	$-NH_2$
470	$-NHCH_2-$		NH_2
471	$-NHCH_2-$		
472	$-NHCH_2-$		
473	$-NHCH_2-$		n-BuNH
474	$-NHCH_2-$		MeO(CH2)$_2$NH
475	$-NHCH_2-$		

Cpd	J	X	Y
476	$-NHCH_2-$		
477	$-NHCH_2-$		
478	$-NHCH_2-$		
479	$-NHCH_2-$		
480	$-NHCH_2-$		
481	$-NHCH_2-$		
482	$-NHCH_2-$		
483	$-NHCH_2-$		Me
484	$-NHCH_2-$		NH_2
and			
485	$-NHCH_2-$		.

[0058] In a second aspect, the novel histone deacetylase inhibitors of the invention are represented by formula (2):



(2)

and pharmaceutically acceptable salts thereof, wherein

Cy^2 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X^1 is selected from the group consisting of a covalent bond, M^1-L^2-M^1, and L^2-M^2-L^2 wherein

L^2, at each occurrence, is independently selected from the group consisting of a chemical bond, C_0-C_4 hydrocarbyl, C_0-C_4-hydrocarbyl-(NH)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(S)-C_0-C_4-hydrocarbyl, and C_0-C_4-hydrocarbyl-(O)-C_0-C_4-hydrocarbyl, provided that L^2 is not a chemical bond when X^1 is M^1-L^2-M^1;

M^1, at each occurrence, is independently selected from the group consisting of -O-, -N(R^7)-, -S-, -S(O)-, $S(O)_2$-, -$S(O)_2N(R^7)$-, -N(R^7)-$S(O)_2$-, -C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-O--and -O-C(O)-NH-, wherein R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, acyl, heterocyclyl, and heteroaryl; and

M^2 is selected from the group consisting of M^1, heteroarylene, and heterocyclylene, either of which rings optionally is substituted;

Ar^2 is arylene or heteroarylene, each of which is optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

q is 0 or 1; and

Ay^2 is a 5-6 membered cycloalkyl, heterocyclyl, or heteroaryl substituted with an amino or hydroxy moiety (preferably these groups are ortho to the amide nitrogen to which Ay^2 is attached) and further optionally substituted;

provided that when Cy^2 is naphthyl, X^1 is $-CH_2-$, Ar^2 is phenyl, R^5 and R^6 are H, and q is 0 or 1, Ay^2 is not phenyl or *o*-hydroxyphenyl.

[0059] In a preferred embodiment of the compounds according to paragraph [0058], when Ay^2 is *o*-phenol optionally substituted by halo, nitro, or methyl, Ar^2 is optionally substituted phenyl, X^1 is -O-, $-CH_2-$, -S-, $-S-CH_2-$, -S(O)-, $-S(O)_2-$, -C(O)-, or $-OCH_2-$, then Cy^2 is not optionally substituted phenyl or naphthyl.

[0060] In another preferred embodiment of the compounds according to paragraph [0058], when Ay^2 is *o*-anilinyl optionally substituted by halo, C_1-C_6-alkyl, C_1-C_6-alkoxy or $-NO_2$, q is 0, Ar^2 is phenyl, and X^1 is $-CH_2-$, then Cy^2 is not substituted pyridone (which substituents of the pyridone are not limited to substituents described herein).

[0061] In another preferred embodiment of the compounds according to paragraph [0058], when X^1 is $-CH_2-$, Ar^2 is optionally substituted phenyl, q is 1, and R^6 is H, then Cy^2 is not optionally substituted imidazole.

[0062] In another preferred embodiment of the compounds according to paragraph [0058], when Ar^2 is amino or hydroxy substituted phenyl, X^1 is C_0-C_8-alkyl-X^{1a}- C_0-C_8-alkyl, wherein X^{1a} is $-CH_2-$, -O-, -S-, -NH-, -C(O)-, then Cy^2 is not optionally substituted naphthyl or di- or -tetrahydronaphthalene.

[0063] In another preferred embodiment of the compounds according to paragraph [0058], when Ay^2 is *o*-phenol, Ar^2 is substituted phenyl, X^1 is -O-, -S-, $-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, or -C(O)-, and R^5 and R^6 are H, then Cy^2 is not optionally substituted naphthyl.

[0064] In another preferred embodiment of the compounds according to paragraph [0058], when Ay^2 is *o*-anilinyl, q is 0, Ar^2 is unsubstituted phenyl, X^1 is $-CH_2-$, then Cy^2 is not substituted 6-hydroimidazolo[5,4-d]pyridazin-7-one-1-yl or substituted 6-hydroimidazolo[5,4-d]pyridazine-7-thione-1-yl.

[0065] Preferably in the compounds according to paragraph [0058], Ay^2 is phenyl or thienyl, each substituted with -OH or $-NH_2$.

[0066] More preferably in the compounds according to paragraph [0058], Ay^2 is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay^2 is attached.

[0067] More preferably in the compounds according to paragraph [0058], Ay^2 is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

[0068] In a another embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0058] wherein

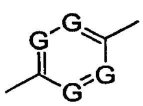
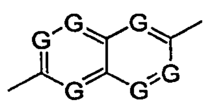
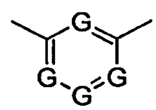
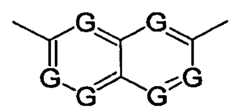
q is 1;

M^1, at each occurrence, is selected from the group consisting of $-N(R^7)-$, $-S-$, $-C(O)-NH-$, and $-O-C(O)-NH-$, where R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl; and

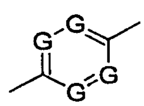
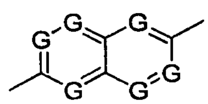
Ay^2 is anilinyl, which optionally is substituted.

[0069] In some preferred embodiments of the compounds according to paragraph [0068], the $-NH_2$ group of Ay^2 is in an ortho position with respect to the nitrogen atom to which Ay^2 is attached. In some embodiments, R^5 and R^6 are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl. In some preferred embodiments, R^5 and R^6 are hydrogen.

[0070] In some embodiments of the compounds according to paragraph [0068], Ar^2 has the formula

, , , or 

wherein G, at each occurrence, is independently N or C, and C optionally is substituted. In some preferred embodiments, Ar^2 has the formula

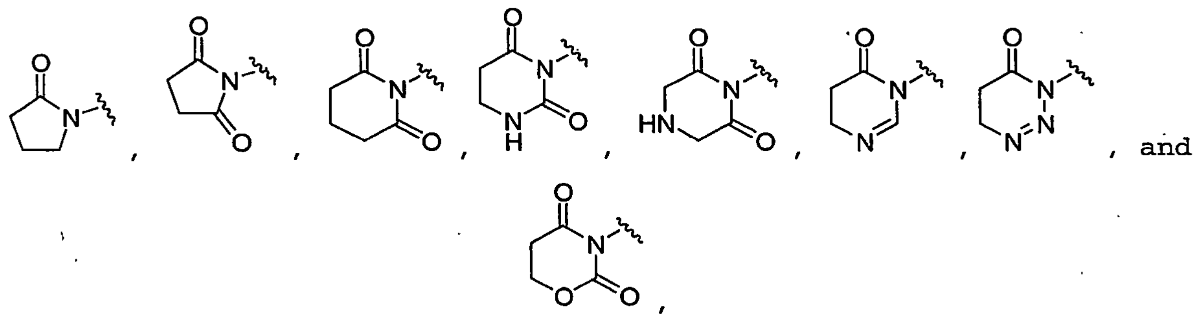
 or .

[0071] In some preferred embodiments of the compounds according to paragraph [0070], Ar^2 is selected from the group consisting of phenylene, pyridylene, pyrimidylene, and quinolylene.

[0072] In some embodiments of the compounds according to paragraph [0068], X^1 is a chemical bond. In some embodiments, X^1 is L^2-M^2-L^2, and M^2 is selected from the group consisting of $-NH-$, $-N(CH_3)-$, $-S-$, $-C(O)-N(H)-$, and $-O-C(O)-N(H)-$. In some embodiments, X^1 is L^2-M^2-L^2, where at least one occurrence of L^2 is a chemical bond. In other embodiments, X^1 is L^2-M^2-L^2, where at least one occurrence of L^2 is alkylene, preferably methylene. In still other embodiments, X^1 is L^2-

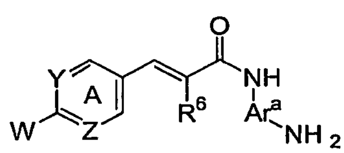
M^2-L^2, where at least one occurrence of L^2 is alkenylene. In some embodiments, X^1 is M^1-L^2-M^1 and M^1 is selected from the group consisting of -NH-, -N(CH_3)-, -S-, and -C(O)-N(H)-.

[0073] In some embodiments of the compounds according to paragraph [0068], Cy^2 is aryl or heteroaryl, *e.g.*, phenyl, pyridyl, imidazolyl, or quinolyl, each of which optionally is substituted. In some embodiments, Cy^2 is heterocyclyl, *e.g.*,



each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy^2 has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl.

[0074] In a preferred embodiment of the compounds of paragraph [0058], the invention comprises compounds of structural formula (2a):



(2a)

and pharmaceutically acceptable salts thereof, wherein

Ar^a is phenyl or thienyl;

R^6 is H, or C_1-C_6-alkyl (preferably --CH_3);

Y and Z are independently -CH= or -N=;

W is halo, $(V'$-$L^4)_t$-V-L^3-;

L^3 is a direct bond, -C_1-C_6-hydrocarbyl, -(C_1-C_3-hydrocarbyl)$_{m1}$-X'-(C_1-C_3- hydrocarbyl)$_{m2}$, -NH-(C_0-C_3-hydrocarbyl), (C_1-C_3-hydrocarbyl)-NH-, or -NH-(C_1-C_3- hydrocarbyl)-NH-;

m1 and m2 are independently 0 or 1;

X' is -N(R^{21})-, -C(O)N(R^{21})-, N(R^{21})C(O)-, -O-, or -S-;

R^{21} is -H, V''-(C_1-C_6-hydrocarbyl)$_c$;

L^4 is (C_1-C_6-hydrocarbyl)$_a$-M-(C_1-C_6-hydrocarbyl)$_b$;

a and b are independently 0 or 1;

M is -NH-, -NHC(O)-, -C(O)NH-, -C(O)-, -SO_2-, -$NHSO_2$-, or -SO_2NH-

V, V', and V" are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

t is 0 or 1;

or W, the annular C to which it is bound, and Y together form a monocyclic cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

wherein the *A* and Ar^a rings are optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

[0075] In a preferred embodiment of the compound according to paragraph [0074]:

Y and Z are –CH= and R^6 is H;

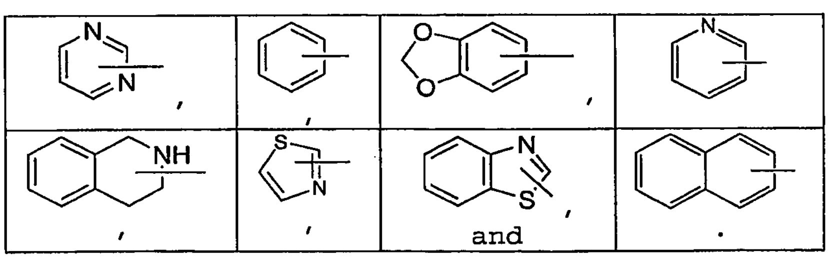
W is V-L^3;

L^3 is -NH-CH- or –CH-NH-;

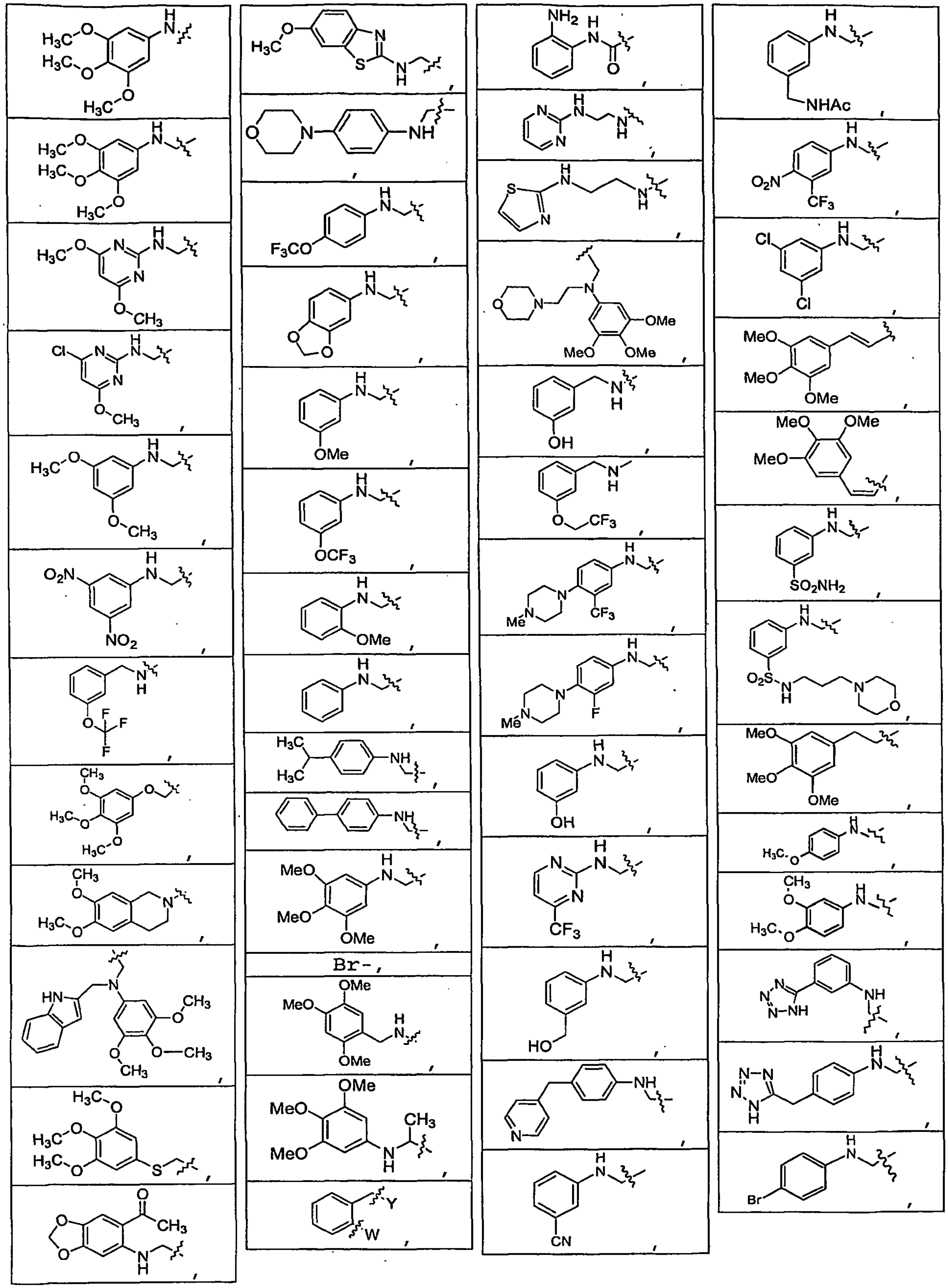
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy, C_1-C_6-hydrocarbyl, C_1-C_6-hydrocarbyl-oxy or -thio (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitroso, amino, sulfonamido, and cyano; and

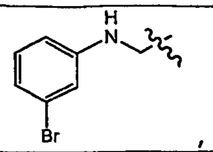
Ar^a is phenyl and the amino moieties to which it is bound are ortho to each other.

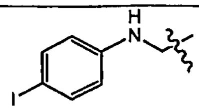
[0076] In some preferred embodiments of the compound according to paragraph [0074], V is an optionally substituted ring moiety selected from:

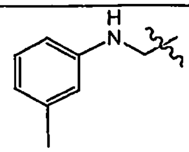


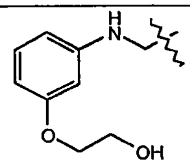
[0077] In another preferred embodiment of the compounds according to paragraph [0074], W is selected from:,

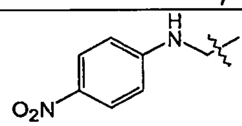

Br-,

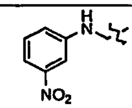
,

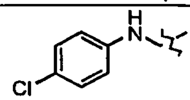
,

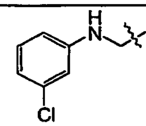
,

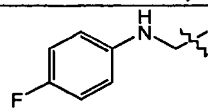
,

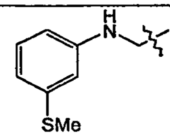
,

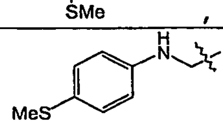
,

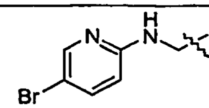
,

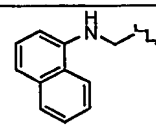
,

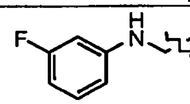
,

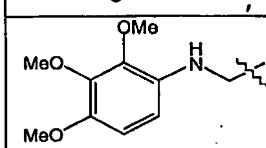
,

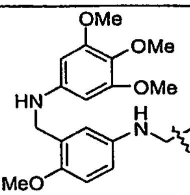
,

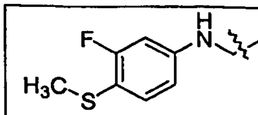
,

,

,

,

,

,

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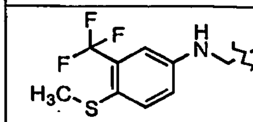
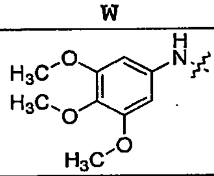
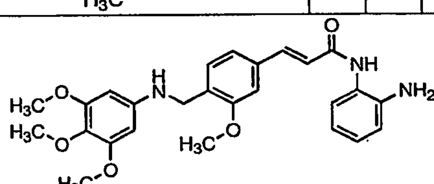
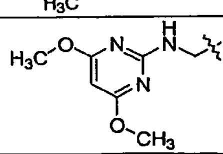
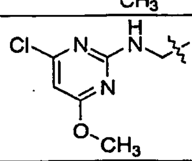
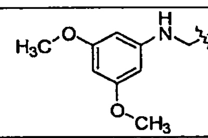
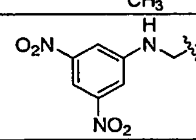
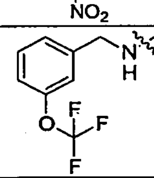
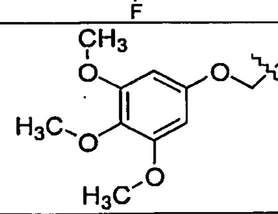
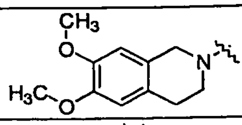
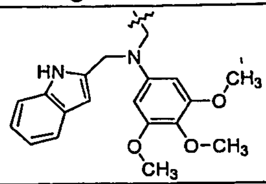
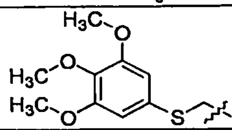
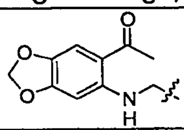
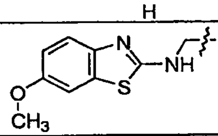
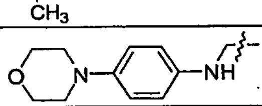
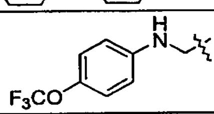
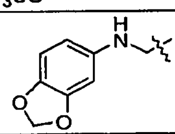
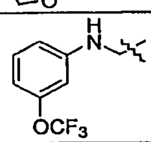
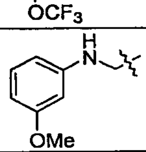
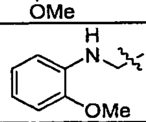
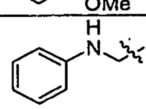
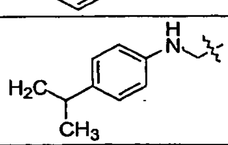
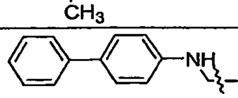
.

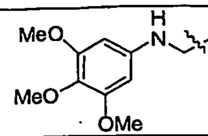
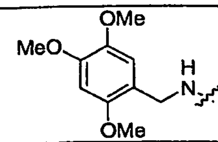
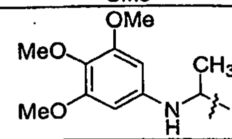
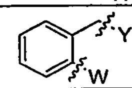
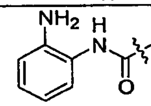
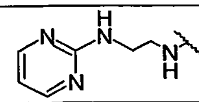
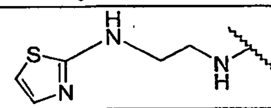
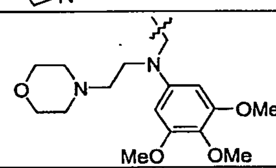
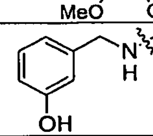
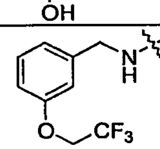
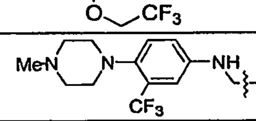
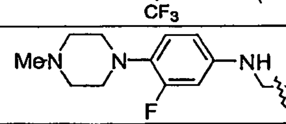
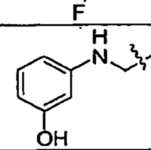
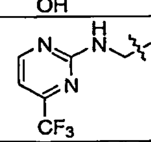
[0078] In another preferred embodiment of the compounds according to paragraph [0074], the *A* and Ar^a rings are not further substituted.

[0079] In a particularly preferred embodiment of the compounds according to paragraph [0074], the compounds of the invention are selected from the following, in which, unless expressly displayed otherwise, Ar^a is phenyl (and, preferably, the amide nitrogen and the amino nitrogen bound to Ar^a are *ortho* to each other):

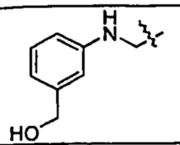
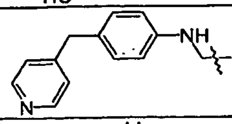
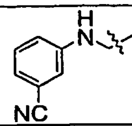
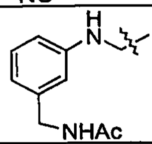
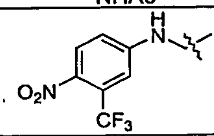
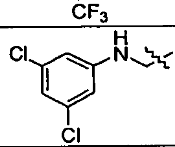
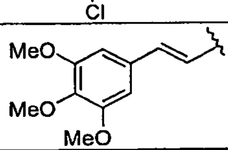
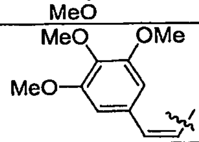
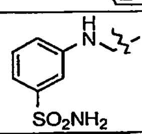
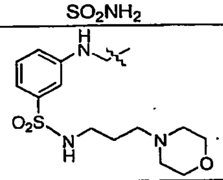
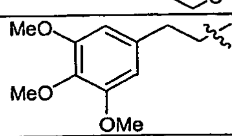
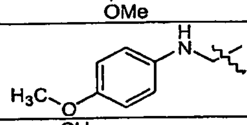
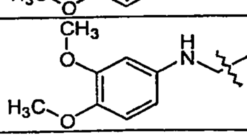
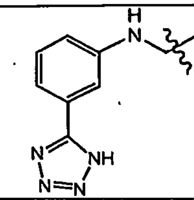
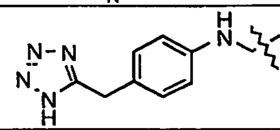
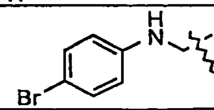
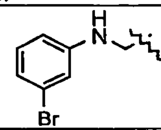
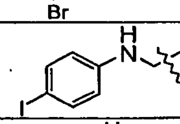
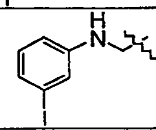
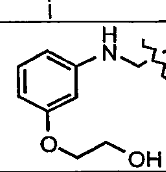
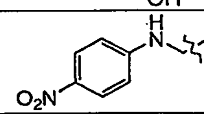
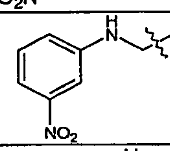
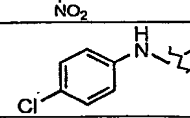
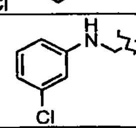
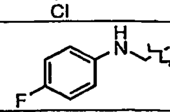
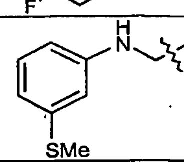
Cpd	W	Y	Z	R^6
481		CH	CH	H
484				
492		CH	CH	H
493		CH	CH	H

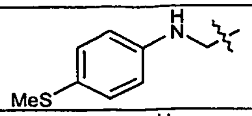
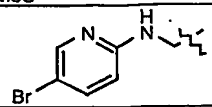
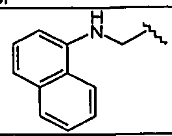
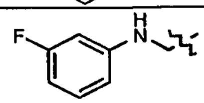
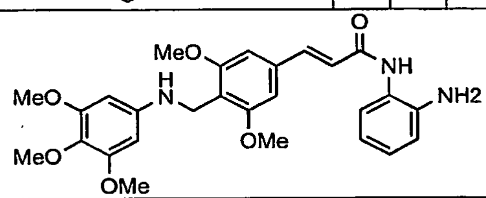
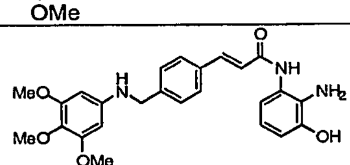
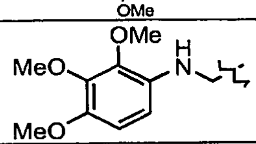
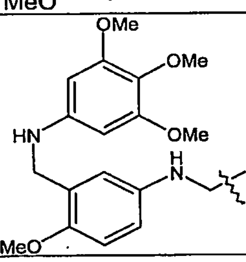
Cpd	W	Y	Z	R^6
494		CH	CH	H
495		CH	CH	H
496		CH	CH	H
497		CH	CH	H

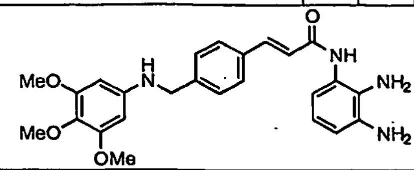
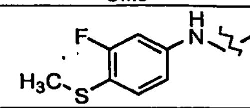
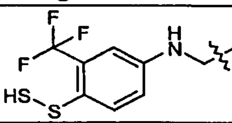
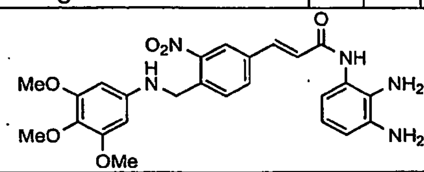
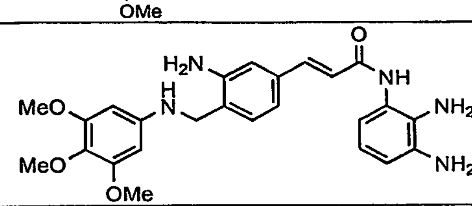
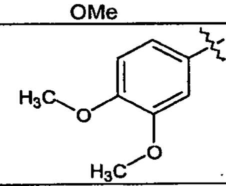
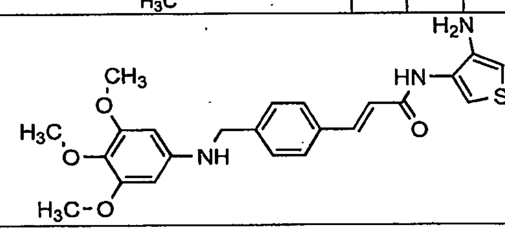
Cpd	W	Y	Z	R^6
498		CH	CH	H
499		CH	CH	H
500		CH	CH	H
501		CH	CH	H
502		CH	CH	H
503		CH	CH	H
504		CH	CH	H
505		CH	CH	H
506		CH	CH	H
507		CH	CH	H
508		CH	CH	H
509		CH	CH	H
510		CH	CH	H
511		CH	CH	H

Cpd	W	Y	Z	R^6
512		CH	N	H
516	Br-	CH	CH	CH_3
517		CH	CH	CH_3
518		CH	CH	CH_3
519		CH	CH	H
520		CH	CH	H
521		N	CH	H
522		N	CH	H
523		CH	CH	H
524		N	CH	H
525		N	CH	H
526		CH	CH	H
527		CH	CH	H
528		CH	CH	H
529		CH	CH	H

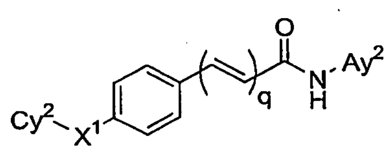
SUBSTITUTE SHEET (RULE 26)

Cpd	W	Y	Z	R^6
530		CH	CH	H
531		CH	CH	H
532		CH	CH	H
533		CH	CH	H
534		CH	CH	H
535		CH	CH	H
536		CH	CH	H
537		CH	CH	H
538		CH	CH	H
539		CH	CH	H
540		CH	CH	H
541		CH	CH	H
542		CH	CH	H
543		CH	CH	H
544		CH	CH	H
545		CH	CH	H
546		CH	CH	H
547		CH	CH	H
548		CH	CH	H
549		CH	CH	H
550		CH	CH	H
551		CH	CH	H
552		CH	CH	H
553		CH	CH	H
554		CH	CH	H
555		CH	CH	H

Cpd	W	Y	Z	R6
556		CH	CH	H
557		CH	CH	H
558		CH	CH	H
559		CH	CH	H
560				
561				
562		CH	CH	H
563		CH	CH	H

Cpd	W	Y	Z	R6
564				
565		CH	CH	H
566		CH	CH	H
567				
568				
569		CH	N	H
570				

[0080] In a preferred embodiment, the compounds of the invention comprise compounds of the formula (2b):



(2b)

and pharmaceutically acceptable salts thereof, wherein

Ay^2 is phenyl or thienyl, each substituted at the ortho position with $-NH_2$ or -OH and each further optionally substituted with one to three substituents independently selected from $-NH_2$, -OH, and halo;

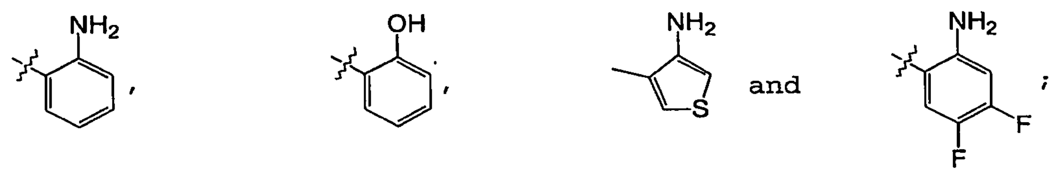
q is 0 or 1;

X^1 is selected from $-CH_2-$, $-NH-CH_2-$, and $-S-CH_2-$;

Cy^2 is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH_3-, CH_3O-, phenyl optionally substituted with one to three CH_3O-, morphylinyl, morphylinyl-C_1-C_3-alkoxy, cyano, and $CH_3C(O)NH-$;

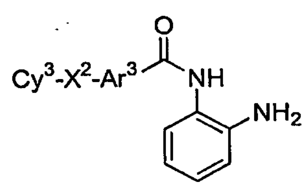
provided that when Cy^2 is naphthyl, X^1 is $-CH_2-$, and q is 0 or 1, Ay^2 is not *o*-hydroxyphenyl.

[0081] Preferably in the compounds according to paragraph [0080], Ay^2 is selected from:



[0082] Preferably in the compounds according to paragraph [0080], Cy^2 is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinozolinyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three CH_3O-. More preferably, Cy^2 is phenyl substituted with one to three CH_3O-.

[0083] In a third embodiment, the novel inhibitors of histone deacetylase are represented by formula (3):



(3)

and pharmaceutical salts thereof, wherein

Ar^3 is arylene or heteroarylene, either of which optionally is substituted;

Cy^3 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted;

provided that when Cy^3 is a cyclic moiety having $-C(O)-$, $-C(S)-$, $-S(O)-$, or $-S(O)_2-$ in the ring, then Cy^3 is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

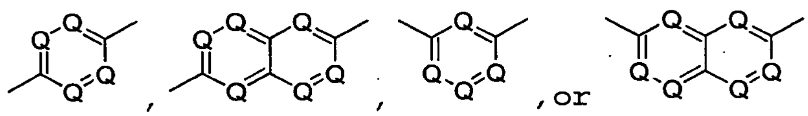
X^2 is selected from the group consisting of a chemical bond, L^3, W^1-L^3, L^3-W^1, $W^1-L^3-W^1$, and $L^3-W^1-L^3$, wherein

W^1, at each occurrence, is S, O, or $N(R^9)$, where R^9 is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

L^3 is C_1-C_4 alkylene, C_2-C_4 alkenylene, or C_2-C_4 alkynylene; provided that X^2 does not comprise a -C(O)-, -C(S)-, -S(O)-, or $-S(O)_2-$ group;

and further provided that when Cy^3 is pyridine, then X^2 is L^3, W^1-L^3, or L^3-W^1.

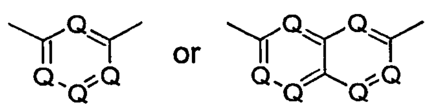
[0084] Preferably, Ar^3 has the structure:



wherein Q, at each occurrence, is independently N or C, and C optionally is substituted.

[0085] Preferably in the compounds according to paragraph [0083], X^2 is selected from the group consisting of L^3, W^1-L^3, L^3-W^1, W^1-L^3-W^1, and L^3-W^1-L^3.

[0086] Preferably in the compounds according to paragraph [0083], when X^2 is a chemical bond, then Ar^3 is not



and Cy^3 is not the radical of a substituted or unsubstituted diazepine or benzofuran.

[0087] In some embodiments of the compounds according to paragraph [0083], Q at each occurrence is $C(R^8)$, where R^8 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. In some other embodiments, from one to about three variables Q are nitrogen. In some preferred embodiments, Ar^3 is selected from the group consisting of phenylene, pyridylene, thiazolylene, and quinolylene.

[0088] In some embodiments of the compounds according to paragraph [0083], X^2 is a chemical bond. In other embodiments, X^2 is a non-cyclic hydrocarbyl. In some such embodiments, X^2 is alkylene, preferably methylene or ethylene. In other such embodiments, X^2 is alkenylene or alkynylene. In still other such embodiments, one carbon in the hydrocaryl chain is replaced with -NH- or -S-. In some preferred embodiments, X^2 is W^1-L^3-W^1 and W^1 is -NH- or $-N(CH_3)-$.

[0089] In some embodiments of the compounds according to paragraph [0083], Cy^3 is cycloalkyl, preferably cyclohexyl. In other embodiments, Cy^3 is aryl or heteroaryl, *e.g.*, phenyl, pyridyl, pyrimidyl, imidazolyl, thiazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the cyclic moiety of Cy^3 is fused to a benzene ring. In some embodiments, Cy^3 has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl. Some other preferred substituents have the formula $-K^1-N(H)(R^{10})$, wherein

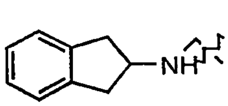
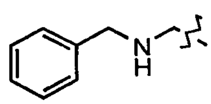
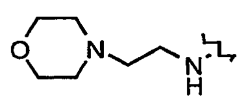
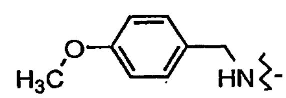
K^1 is a chemical bond or C_1-C_4 alkylene;

R^{10} is selected from the group consisting of Z' and $-Ak^2-Z'$, wherein

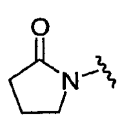
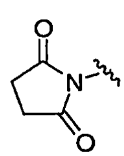
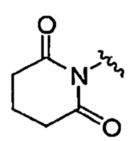
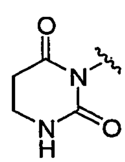
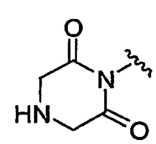
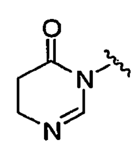
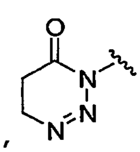
Ak^2 is C_1-C_4 alkylene; and

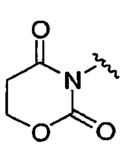
Z' is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings.

[0090] Examples of such preferred substituents according to paragraph [0089] include

, , , and .

[0091] In some embodiments of the compounds according to paragraph [0083], Cy^3 is heterocyclyl, *e.g.*,

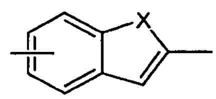
, , , , , , , and

,

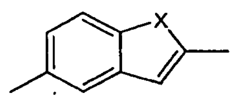
each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the heterocycle of Cy^3 is fused to a benzene ring.

[0092] Preferably in the compounds of paragraph [0083], when Ar^4 is quinoxalinylene, then X^3 is not -CH(OH)-.

[0093] In another preferred embodiment, Ar^3 is



wherein X is $-CH_2-$, -NH-, O, or S. Preferably Ar^3 is



and X is S or O.

[0094] In a preferred embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0058] wherein

Ay^2 is ortho-anilinyl;

q is 0; and

X^1 is M^1-L^2-M^1 or L^2-M^2-L^2.

[0095] In a preferred embodiment of the compounds according to paragraph [0094], Ar^2 is aryl or heteroaryl; and Cy^2-X^1- is collectively selected from the group consisting of

a) A_1-L_1-B_1-, wherein A_1 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_1 is $-(CH_2)_{0-1}NH(CH_2)_{0-1}-$, -NHC(O)-, or $-NHCH_2-$; and wherein B_1 is phenyl or a covalent bond;

b) A_2-L_2-B_2-, wherein A_2 is $CH_3(C{=}CH_2)-$, optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein L_2 is $-C{\equiv}C-$; and wherein B_2 is a covalent bond;

c) A_3-L_3-B_3-, wherein A_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_3 is a covalent bond; and wherein B_3 is $-CH_2NH-$;

d) A_4-L_4-B_4-, wherein A_4 is an optionally substituted aryl; wherein L_4 is $-NHCH_2-$; and wherein B_4 is a thienyl group;

e) A_5-L_5-B_5-, wherein A_5 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_5 is a covalent bond; and wherein B_5 is -SCH_2-;

f) morpholinyl-CH_2-

g) optionally substituted aryl;

h) A_6-L_6-B_6-, wherein A_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_6 is a covalent bond; and wherein B_6 is -$NHCH_2$-;

i) A_7-L_7-B_7-, wherein A_7 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_7 is a covalent bond; and wherein B_7 is -CH_2-;

j) aptionally substituted heteroaryl or optionally substituted heterocyclyl;

k) A_8L_8-B_8-, wherein A_8 is optionally substituted phenyl; wherein L_8 is a covalent bond; and wherein B_8 is -O-;

l) A_9-L_9-B_9-, wherein A_9 is an optionally substituted aryl; wherein L_9 is a covalent bond; and wherein B_9 is a furan group;

m) A_{10}-L_{10}-B_{10}-, wherein A_{10} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{10} is -$CH(CH_2CH_3)$-; and wherein B_{10} is -$NHCH_2$-;

n) A_{11}-L_{11}-B_{11}-, wherein A_{11} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{11} is a covalent bond; and wherein B_{11} is -OCH_2-;

o) A_{12}-L_{12}-B_{12}-, wherein A_{12} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{12} is-NHC(O)-; and wherein B_{12} is -N(optionally substituted aryl)CH_2-;

p) A_{13}-L_{13}-B_{13}-, wherein A_{12} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{13} is a covalent bond; and wherein B_{13} is -NHC(O)-;

q) A_{14}-L_{14}-B_{14}-, wherein A_{14} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{14} is-NHC(O)(optionally substituted heteroaryl); and wherein B_{14} is -S-S-;

r) $F_3CC(O)NH$-;

s) A_{15}-L_{15}-B_{15}-, wherein A_{15} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{15} is-$(CH_2)_{0-1}$NH(optionally substituted heteroaryl)-; and wherein B_{15} is -$NHCH_2$-;

t) A_{16}-L_{16}-B_{16}-, wherein A_{16} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{16} is a covalent bond; and wherein B_{16} is -N(optionally substituted alkyl)CH_2-; and

u) A_{16}-L_{16}-B_{16}-, wherein A_{16} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{16} is a covalent bond; and wherein B_{16} is -(optionally substituted aryl-CH_2)$_2$-N-.

[0096] In another preferred embodiment of the compounds according to paragraph [0094], Cy^2-X^1- is collectively selected from the group consisting of

a) D_1-E_1-F_1-, wherein D_1 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_1 is -CH_2- or a covalent bond; and wherein B_1 is a covalent bond;

b) D_2-E_2-F_2-, wherein D_2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_2 is -$NH(CH_2)_{0-2}$-; and wherein F_2 is a covalent bond;

c) D_3-E_3-F_3-, wherein D_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_3 is -$(CH_2)_{0-2}NH$-; and wherein F_3 is a covalent bond;

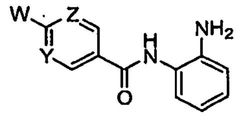
d) D_4-E_4-F_4-, wherein D_4 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_4 is -$S(CH_2)_{0-2}$-; and wherein F_4 is a covalent bond;

e) D_5-E_5-F_5-, wherein D_5 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_5 is -$(CH_2)_{0-2}S$-; and wherein F_5 is a covalent bond; and

f) D_6-E_6-F_6-, wherein D_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted

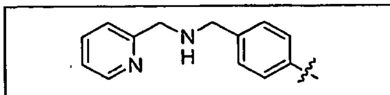
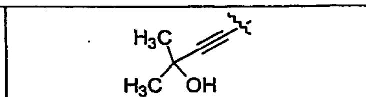
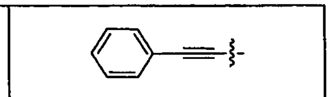
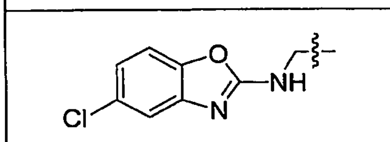
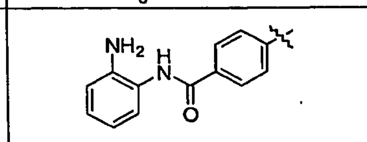
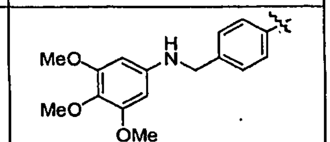
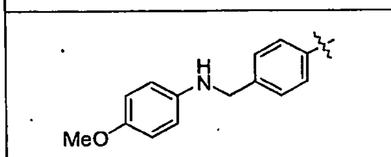
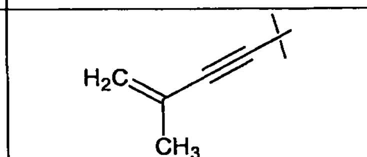
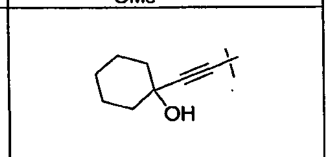
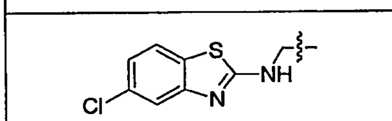
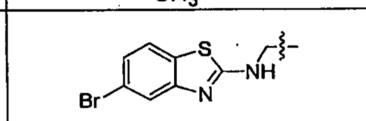
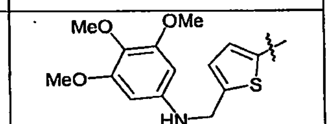
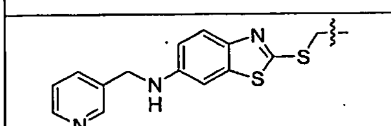
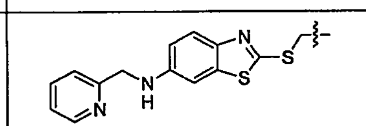
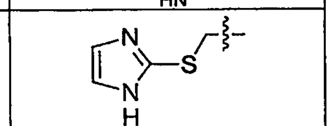
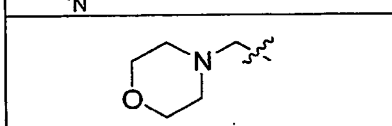
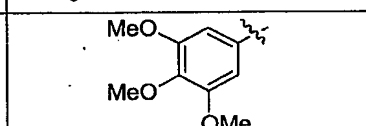
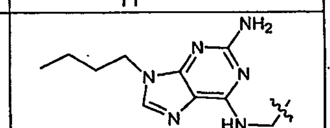
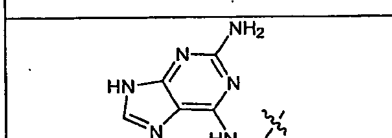
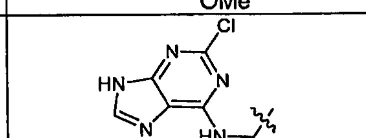
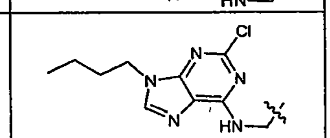
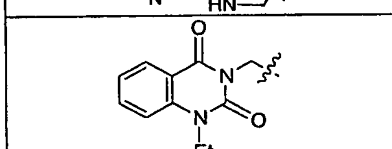
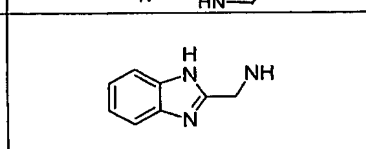
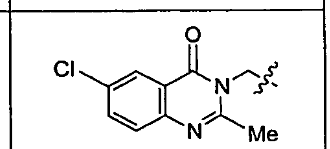
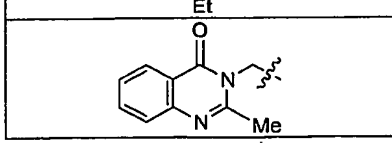
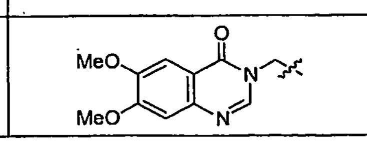
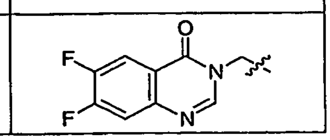
heterocyclyl; wherein E_6 is $-NH(CH_2)_{0-2}NH-$; and wherein F_6 is a covalent bond.

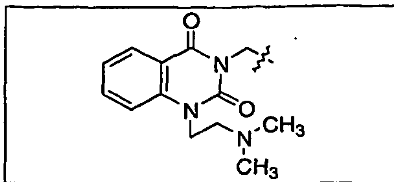
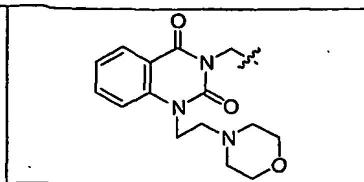
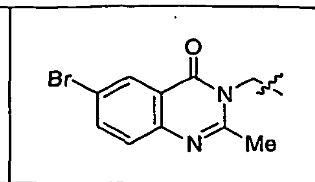
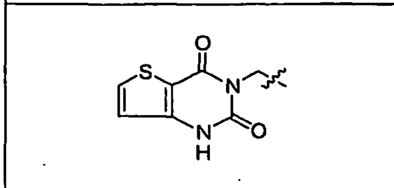
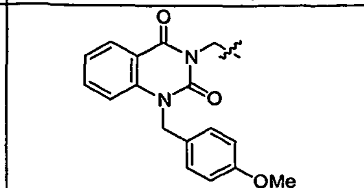
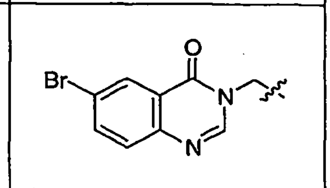
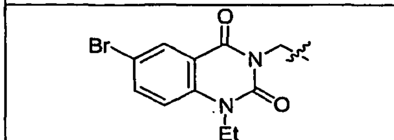
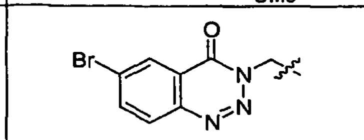
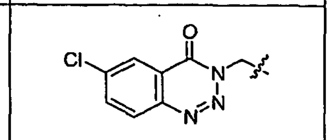
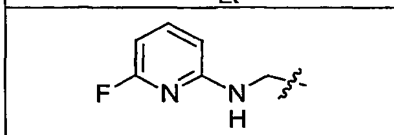
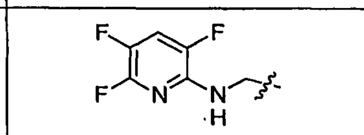
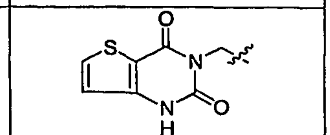
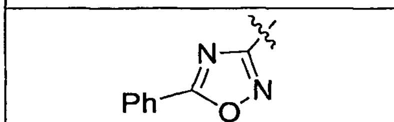
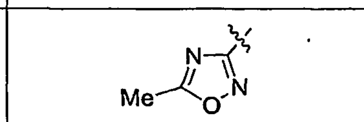
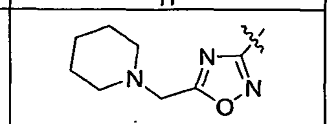
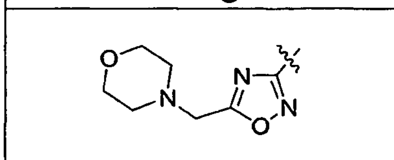
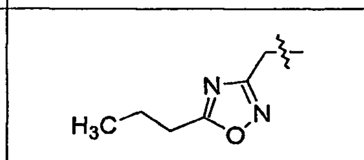
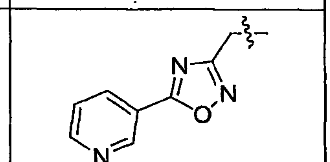
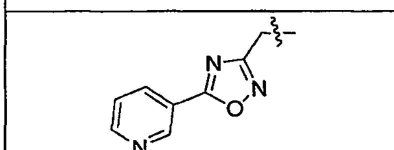
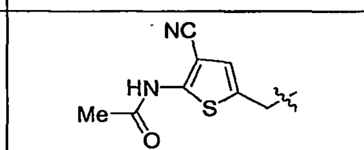
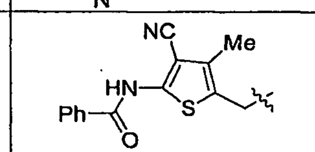
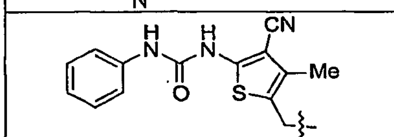
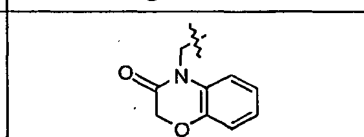
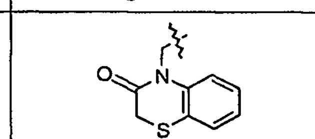
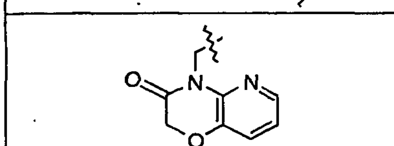
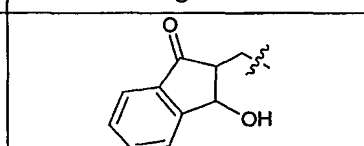
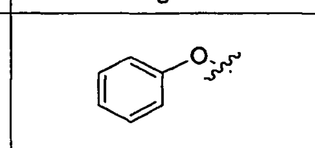
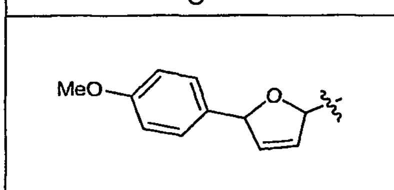
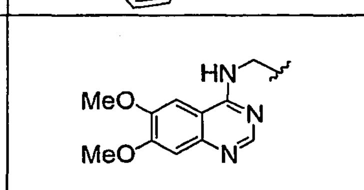
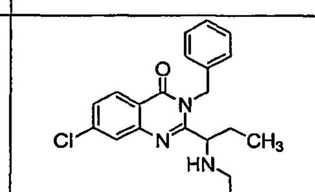
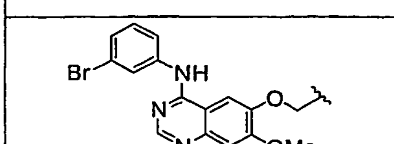
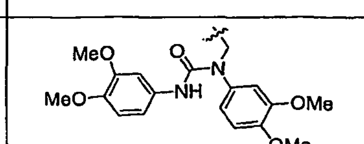
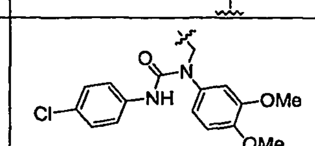
[0097] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0058] having formula (3b):

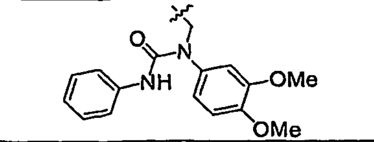
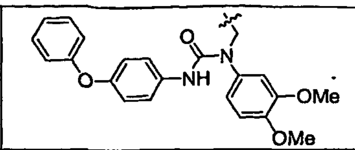
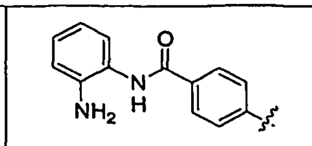
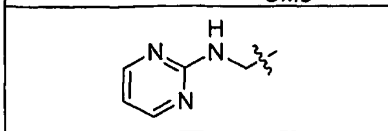
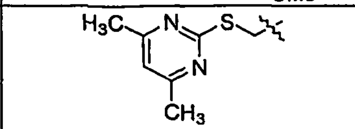
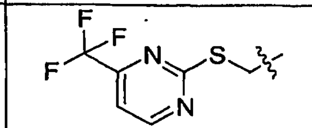
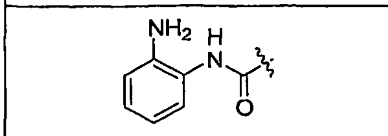
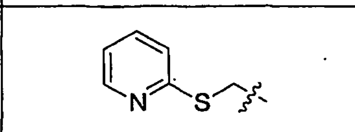
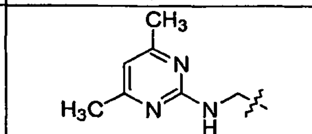
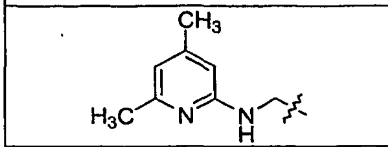
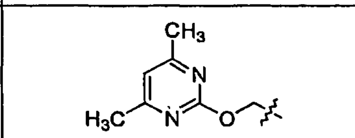
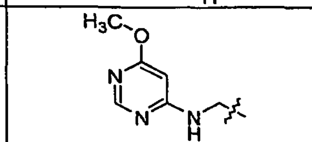
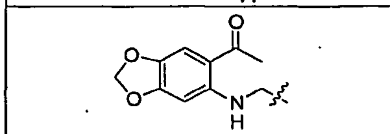
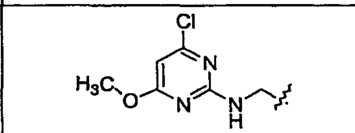
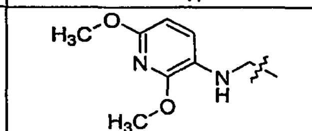
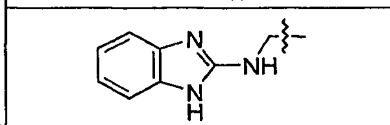
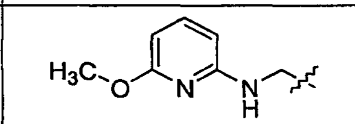
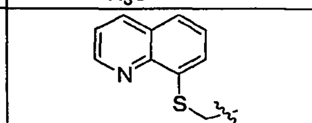
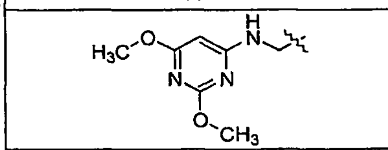
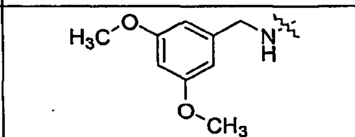
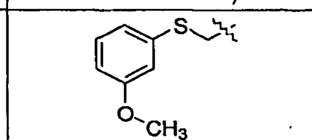
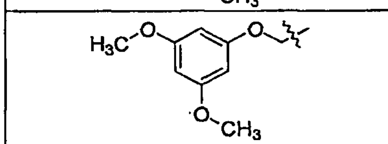
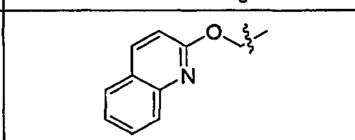
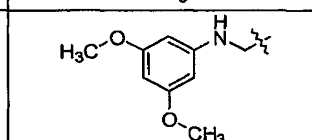
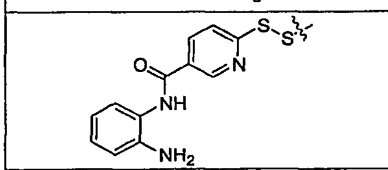
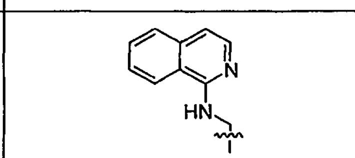
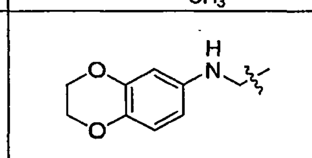
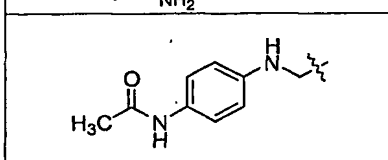
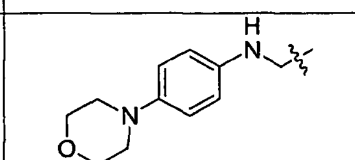
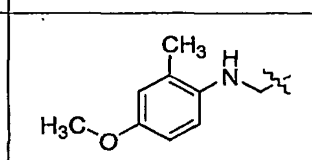
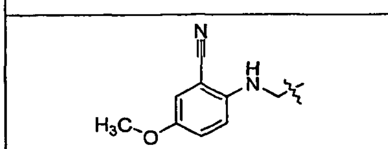
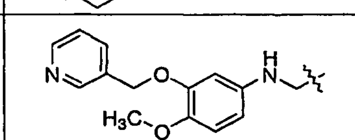
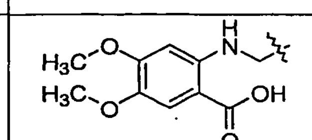
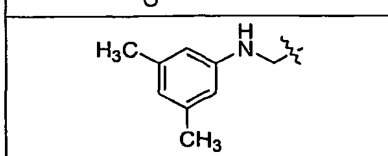
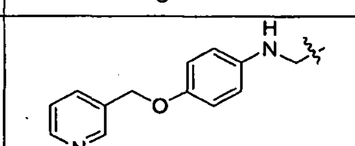
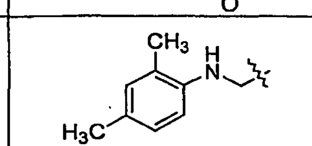


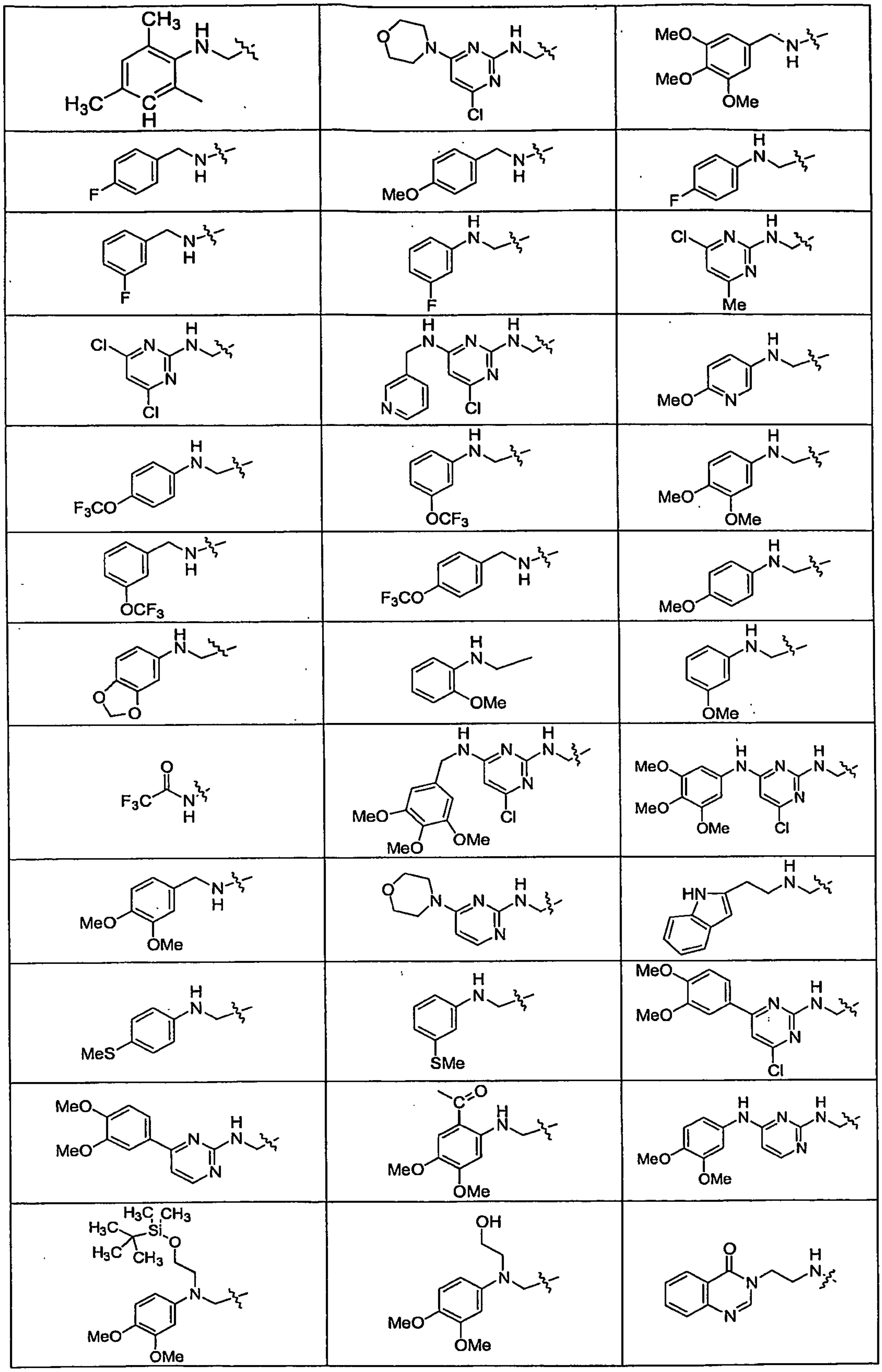
(3b)

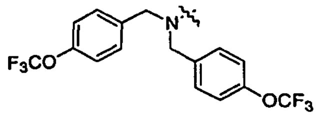
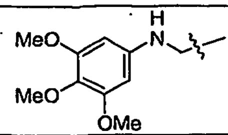
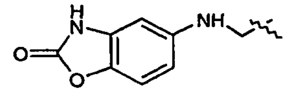
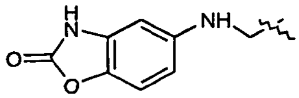
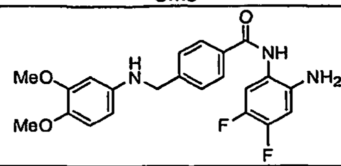
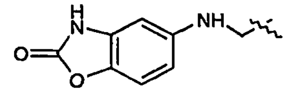
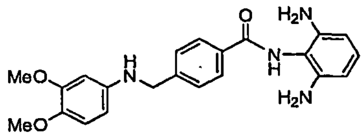
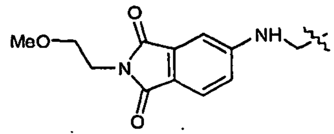
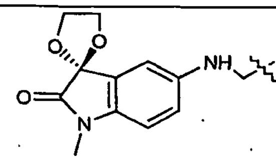
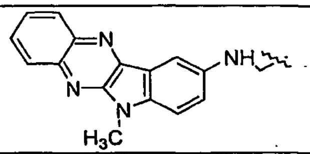
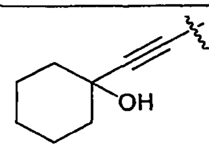
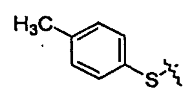
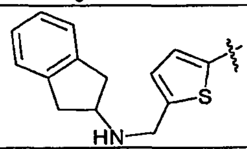
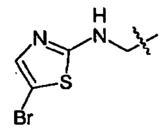
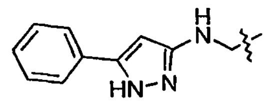
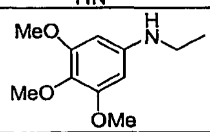
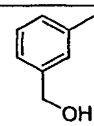
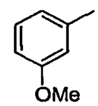
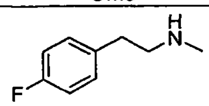
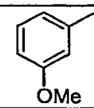
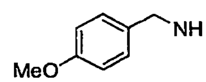
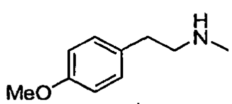
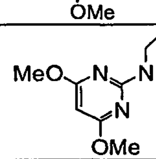
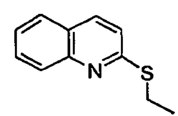
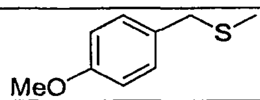
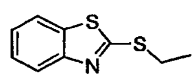
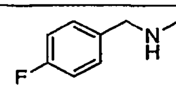
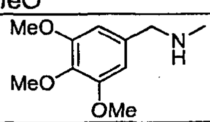
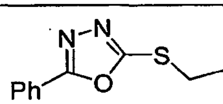
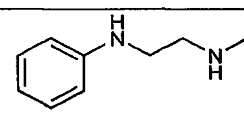
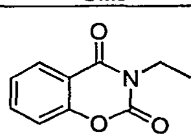
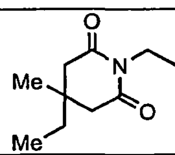
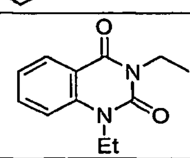
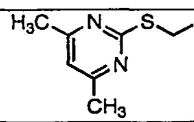
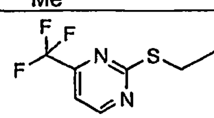
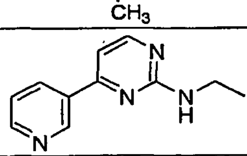
and pharmaceutically acceptable salts thereof, wherein Y and Z are independently N or CH and W is selected from the group consisting of:

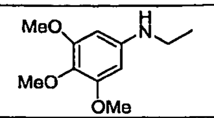
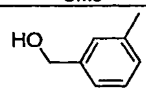
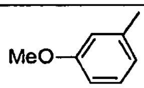
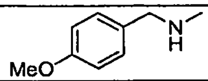
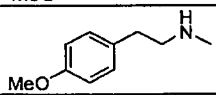
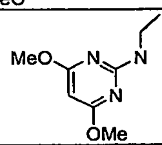
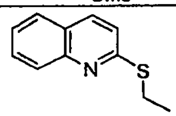
		
		
		
		
		
		
		
		
		
		
		

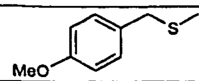
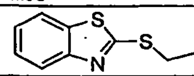
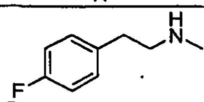
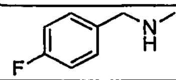
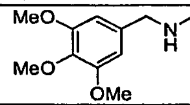
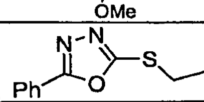
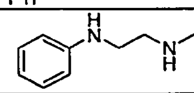
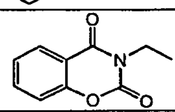
		
		
		
		
		
		
		
		
		
		
		
		

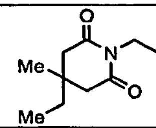
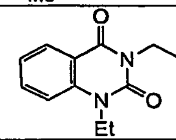
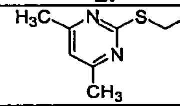
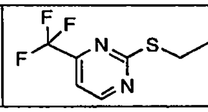


		
		
		
		
		
		
		
		
		
		
		
		and
		

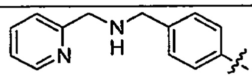
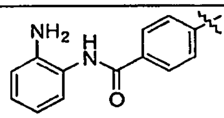
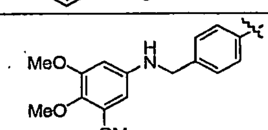
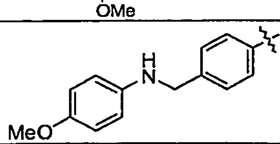
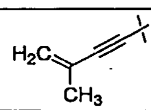
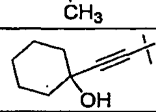
[0098] In a preferred embodiment of the compounds according to paragraph [0097], the compounds comprise those wherein Y, Z and W are as defined below:

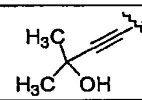
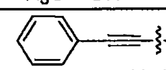
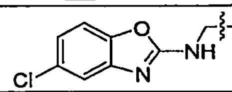
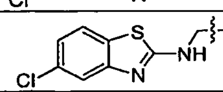
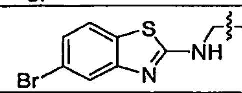
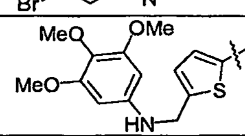
Cpd	W	Y	Z
164		CH	CH
165		N	CH
166		CH	CH
167		CH	N
168		CH	N
169		CH	CH
170		CH	CH

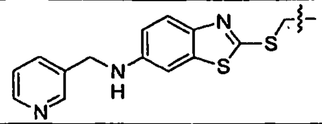
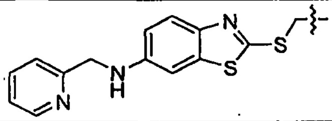
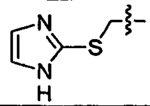
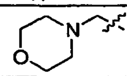
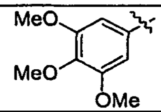
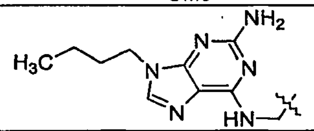
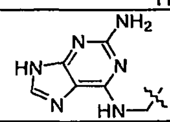
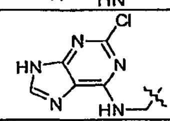
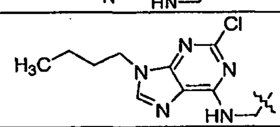
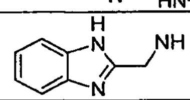
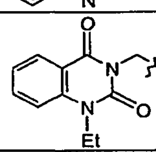
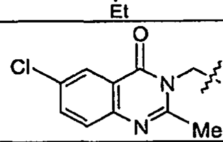
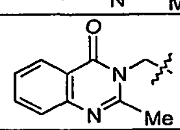
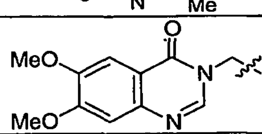
Cpd	W	Y	Z
171		N	CH
172		CH	CH
174		CH	N
175		CH	N
176		CH	N
177		CH	CH
178		N	CH
179		CH	CH

Cpd	W	Y	Z
180		CH	CH
181		CH	CH
182		CH	CH
	and		
183		CH	CH

[0099] In another preferred embodiment of the compounds according to paragraph [0097], the compounds comprise those wherein Y, Z and W are as defined below:

Cpd	W	Y	Z
187		CH	CH
188		CH	CH
189		CH	CH
190		CH	CH
193		CH	CH
194		CH	CH

Cpd	W	Y	Z
195		CH	CH
196		CH	CH
320		CH	CH
321		CH	CH
322		CH	CH
323		CH	CH

Cpd	W	Y	Z
325		CH	CH
326		CH	CH
327		CH	CH
328		CH	CH
329		CH	CH
330		CH	CH
331		CH	CH
332		CH	CH
333		CH	CH
334		CH	CH
335		CH	CH
336		CH	CH
337		CH	CH
338		CH	CH

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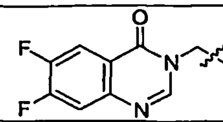
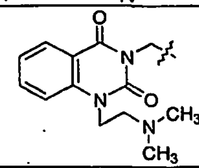
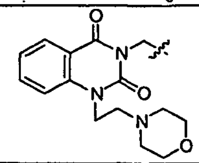
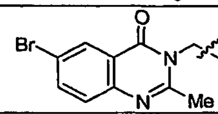
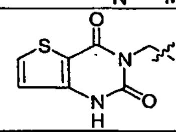
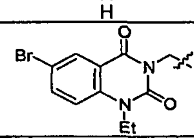
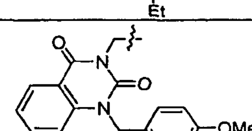
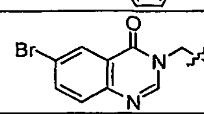
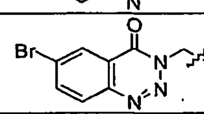
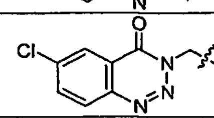
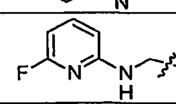
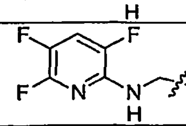
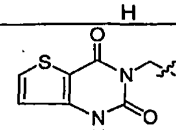
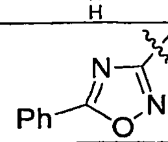
339		CH	CH
340		CH	CH
341		CH	CH
342		CH	CH
343		CH	CH
344		CH	CH
345		CH	CH
346		CH	CH
347		CH	CH
348		CH	CH
349		CH	CH
350		CH	CH
351		CH	CH
352		CH	CH

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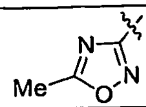
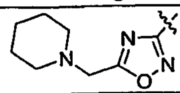
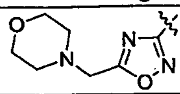
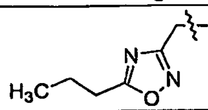
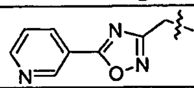
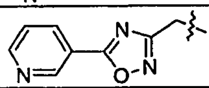
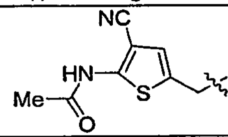
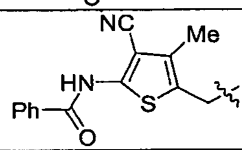
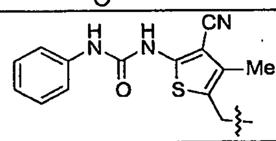
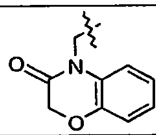
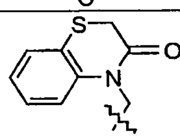
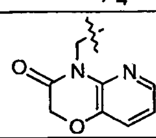
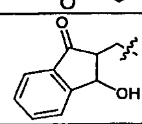
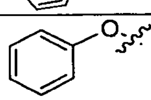
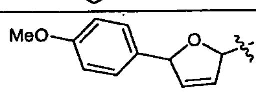
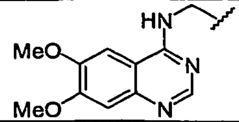
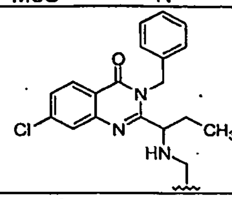
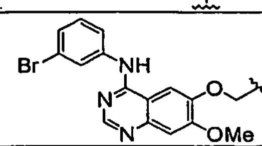
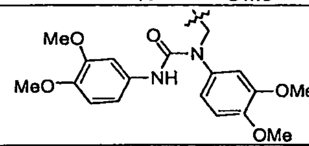
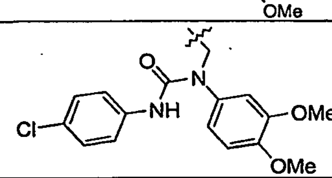
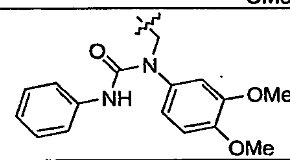
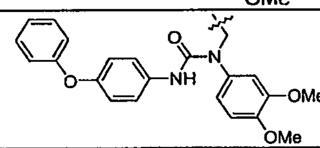
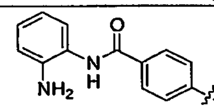
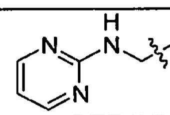
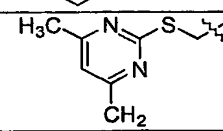
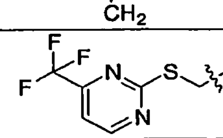
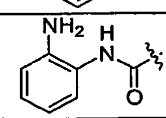
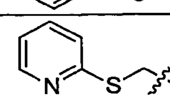
353		CH	CH
354		CH	CH
355		CH	CH
356		CH	CH
357		CH	CH
358		CH	CH
359		CH	CH
360		CH	CH
361		CH	CH
362		CH	CH
363		CH	CH
364		CH	CH
365		CH	CH
366		CH	CH
367		CH	CH
368		CH	CH
369		CH	CH
370		CH	CH
371		CH	CH
372		CH	CH
373		CH	CH
374		CH	CH
375		CH	CH
377		CH	CH
378		CH	CH
379		CH	CH
380		N	CH
381		CH	CH

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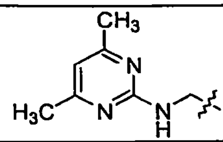
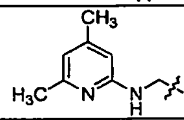
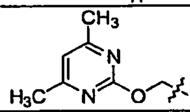
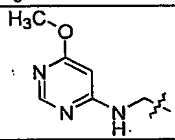
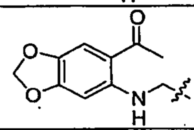
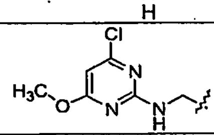
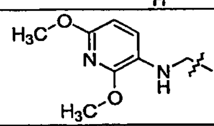
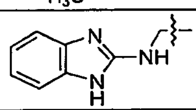
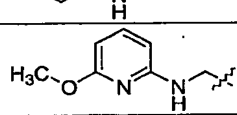
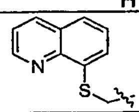
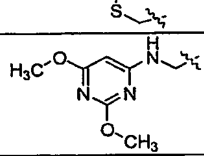
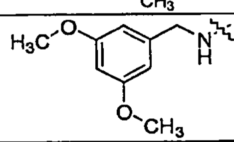
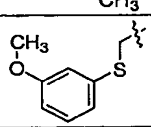
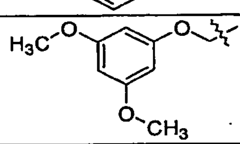
382		CH	CH
383		CH	CH
384		CH	CH
385		CH	CH
386		CH	CH
387		CH	CH
388		CH	CH
389		CH	CH
390		CH	CH
391		CH	CH
392		CH	CH
393		CH	CH
394		CH	CH
395		CH	CH

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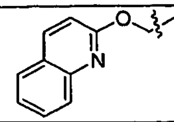
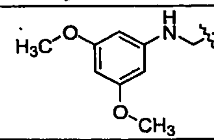
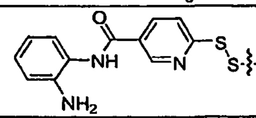
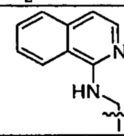
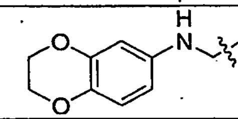
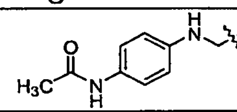
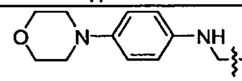
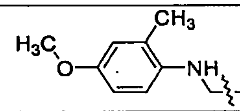
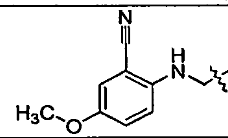
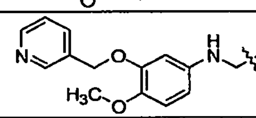
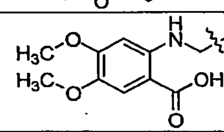
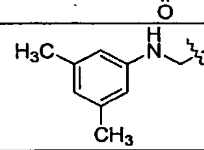
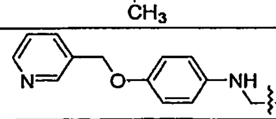
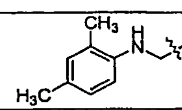
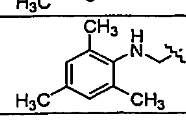
396		CH	CH
397		CH	CH
398		CH	N
399		CH	CH
400		CH	CH
401		CH	CH
402		CH	CH
403		CH	CH
404		CH	CH
405		CH	CH
406		CH	CH
407		CH	CH
408		CH	CH
409		CH	CH
410		CH	CH

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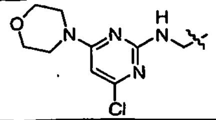
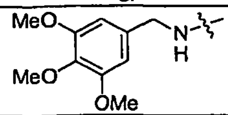
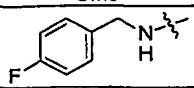
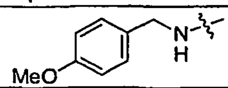
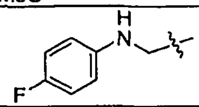
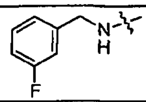
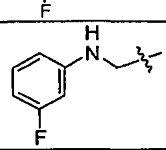
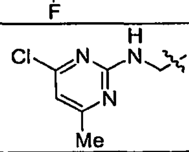
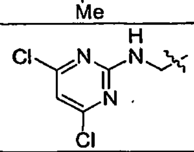
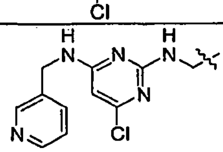
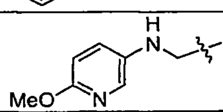
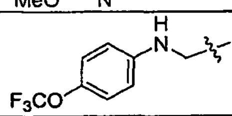
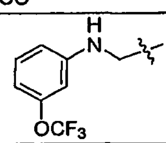
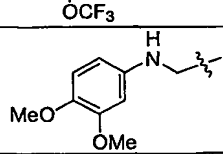
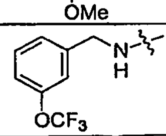
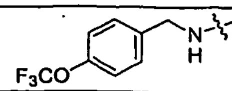
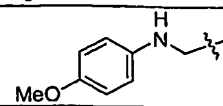
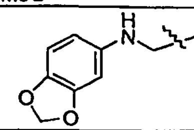
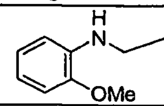
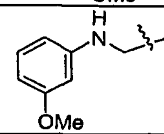
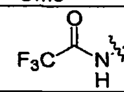
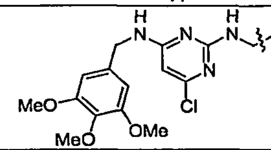
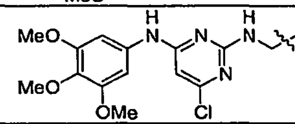
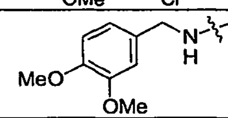
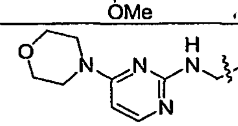
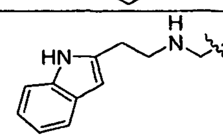
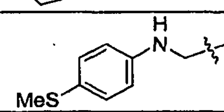
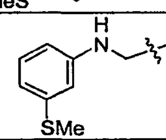
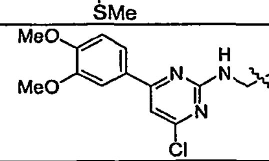
411		CH	CH
412		CH	CH
413		CH	CH
414		CH	CH
415		CH	CH
416		CH	CH
417		CH	CH
418		CH	CH
419		CH	CH
420		CH	CH
421		CH	CH
422		CH	CH
423		CH	CH
424b		CH	CH
425		CH	CH

Cpd	W	Y	Z
426		CH	CH
427		CH	CH
428		CH	CH
429		CH	CH
430		CH	CH
431		CH	CH
432		CH	CH
433		CH	CH
434		CH	CH
435		CH	CH
436		CH	CH
437		CH	CH
438		CH	CH
439		CH	CH

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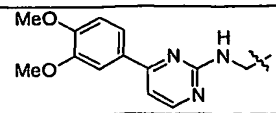
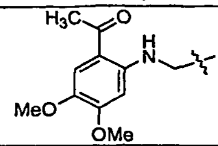
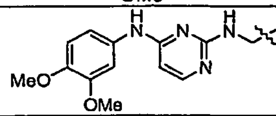
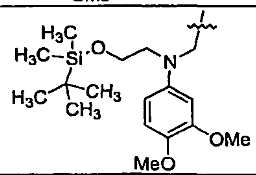
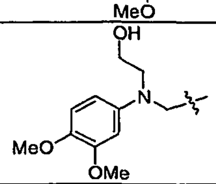
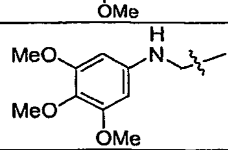
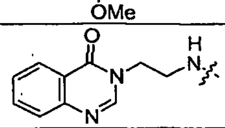
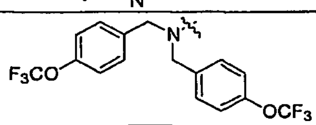
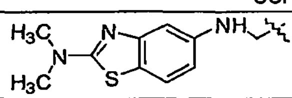
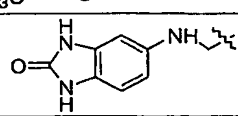
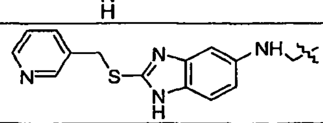
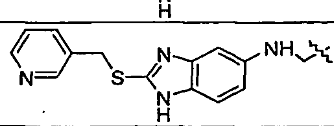
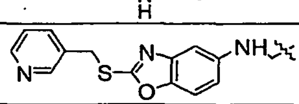
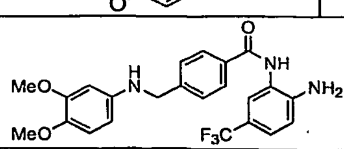
440		CH	CH
441		CH	CH
442		CH	CH
443		CH	CH
444		CH	CH
445		CH	N
446		CH	N
447		CH	CH
448		CH	CH
449		CH	CH
450		CH	CH
451		CH	CH
452		CH	CH
453			

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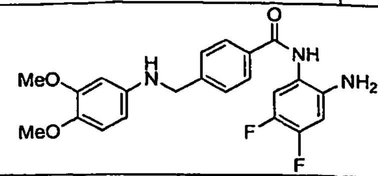
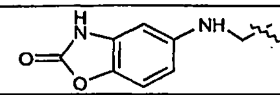
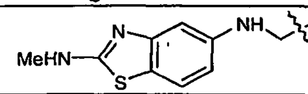
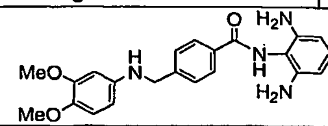
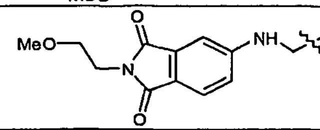
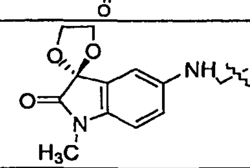
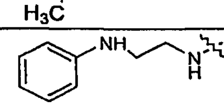
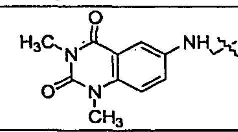
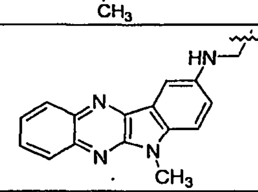
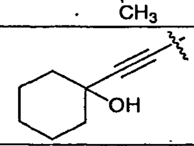
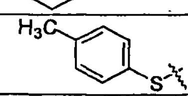
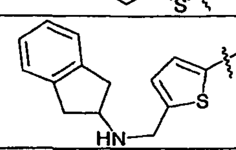
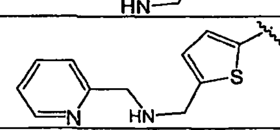
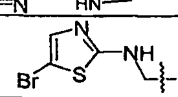
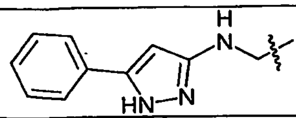
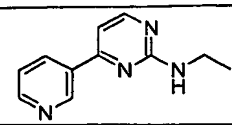
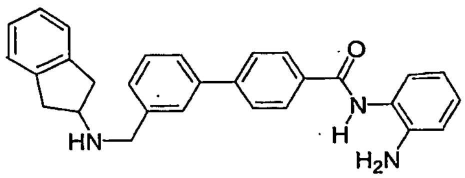
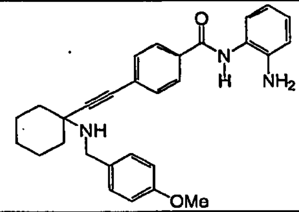
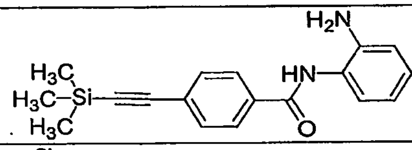
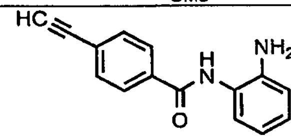
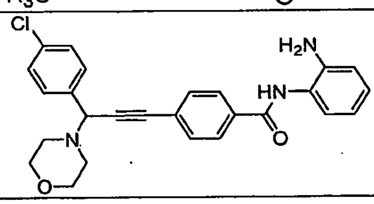
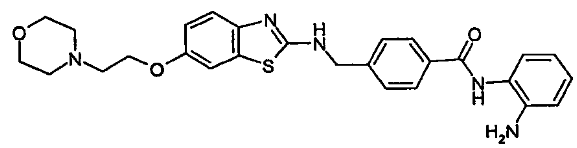
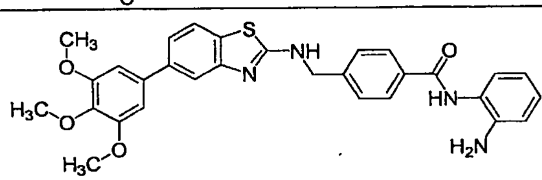
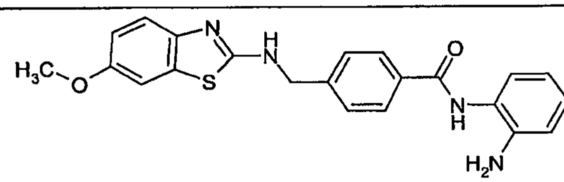
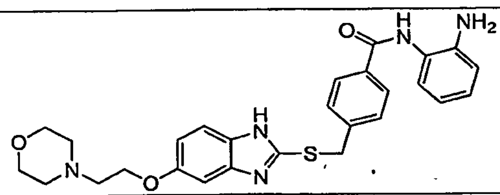
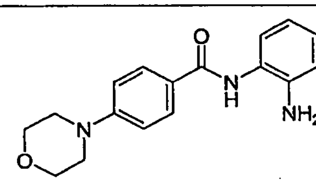
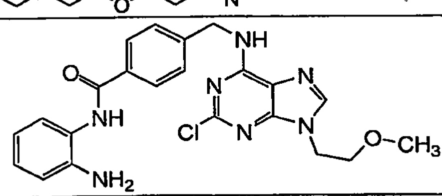
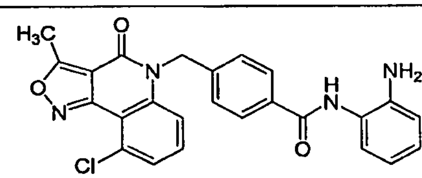
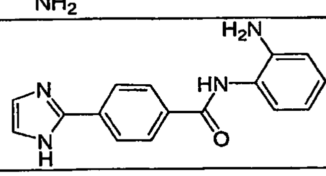
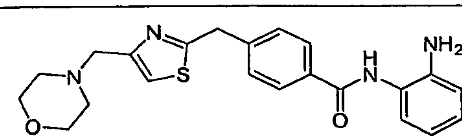
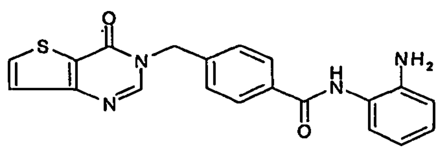
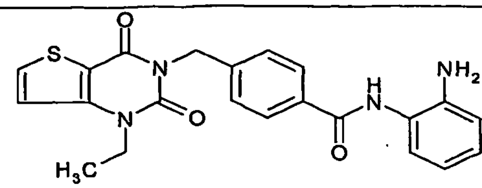
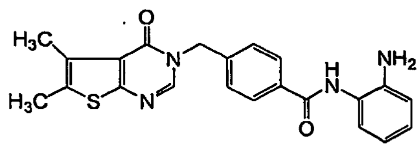
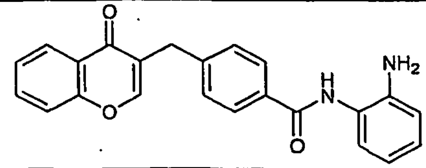
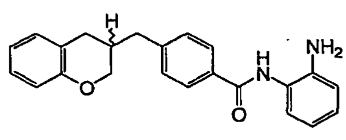
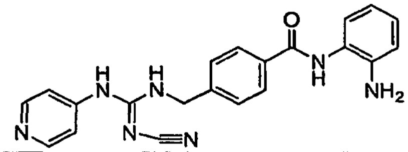
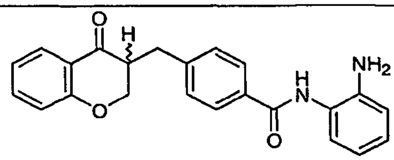
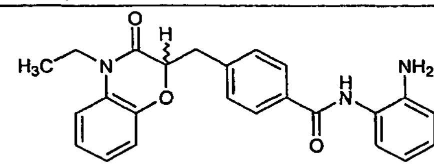
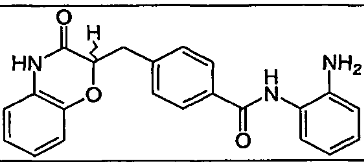
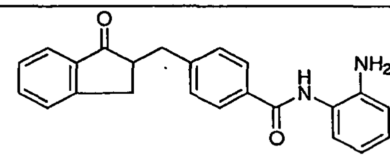
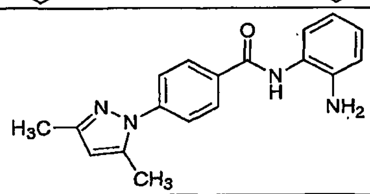
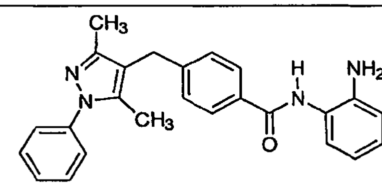
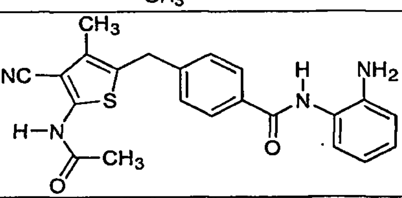
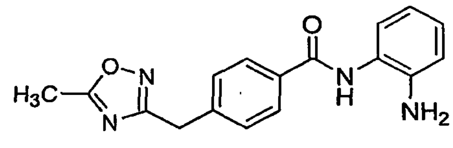
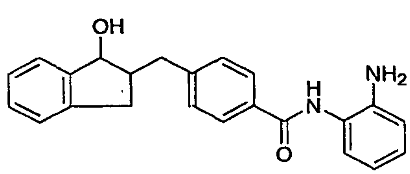
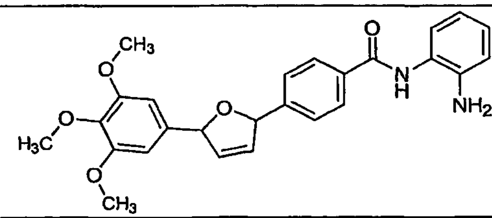
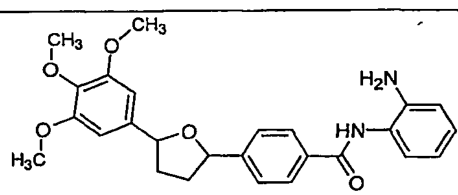
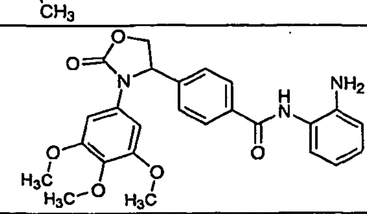
454			
455		CH	CH
456		CH	CH
457			
458		CH	CH
459		CH	CH
460		CH	N
461		CH	CH
462		CH	CH
463		N	CH
464		N	CH
465		CH	CH
466		CH	CH
467		CH	CH

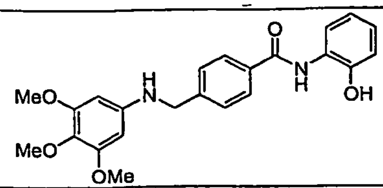
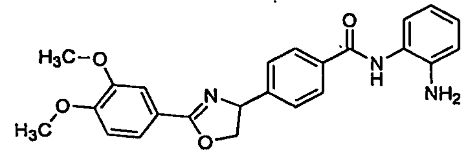
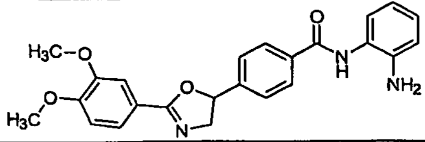
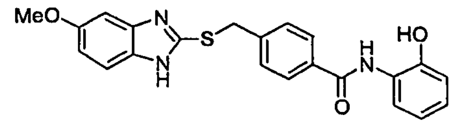
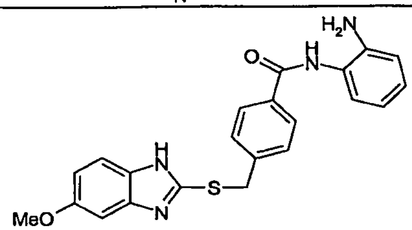
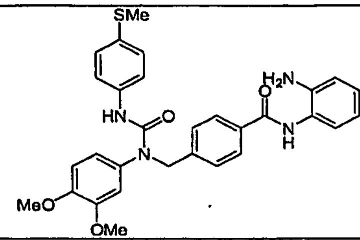
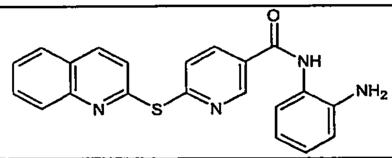
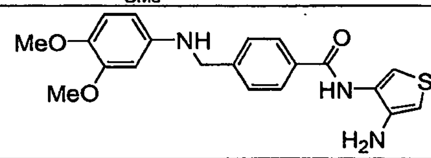
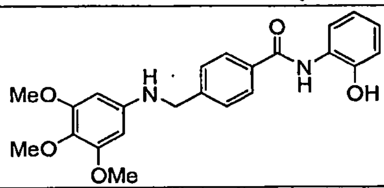
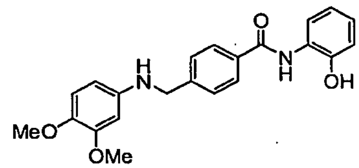
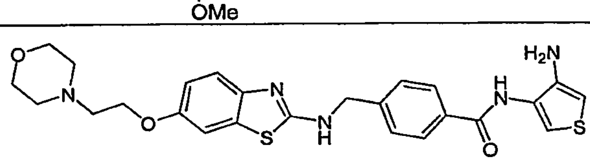
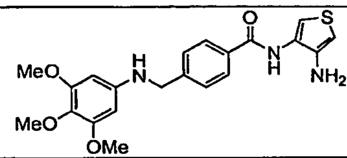
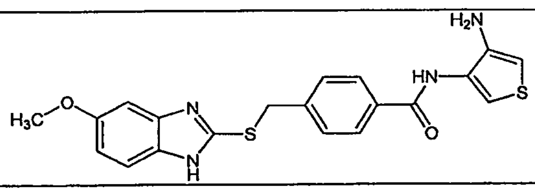
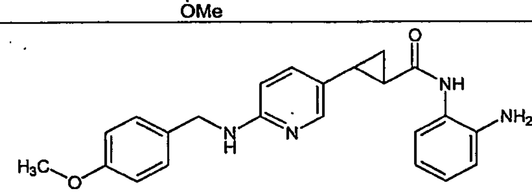
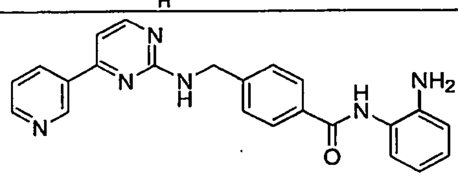
Cpd	W	Y	Z
468		CH	CH

Cpd	W	Y	Z
700		CH	CH

[0100] In yet another a preferred embodiment, the novel histone deacetylase inhibitors of the invention are selected from the group consisting of the following and their pharmaceutically acceptable salts:

[0101] In another preferred embodiment, the compounds are selected from those listed in Tables 2a-b, 3a-d, 4a-c, and 5a-5f.

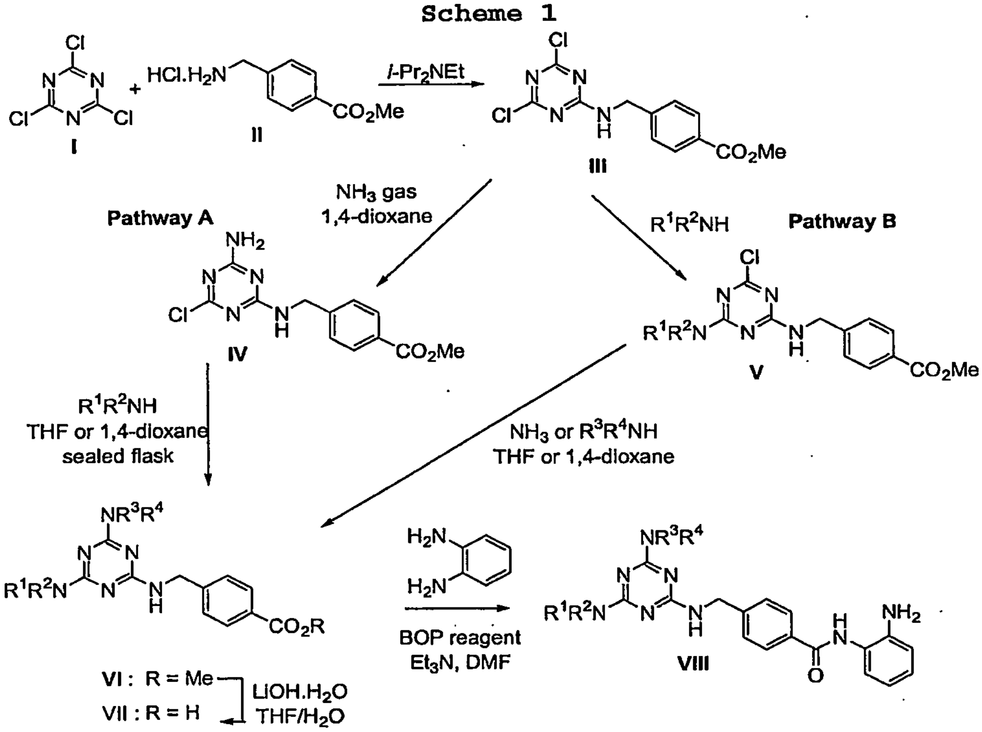
Synthesis

[0102] Compounds of formula (1), wherein Y^1 is $-N(R^1)(R^2)$, preferably may be prepared according to the synthetic route depicted in Scheme 1. Thus, trichlorotriazine **I** reacts with amine **II** in the presence of diisopropylethylamine to produce dichloroaminotriazine **III**. The amine R^1R^2NH is added to dichloroaminotriazine **III** to produce diaminochlorotriazine **V**. Treatment of **V** with ammonia or R^3R^4NH in tetrahydrofuran (THF) or 1,4 dioxane affords triaminotriazine **VI**.

[0103] Alternatively, dichloroaminotriazine **III** may be reacted with ammonia gas in 1,4 dioxane to produce diaminochlorotriazine **IV**. Treatment of **IV** with R^1R^2NH in THF or 1,4 dioxane in a sealed flask then affords triaminotriazine **VI**.

[0104] Hydrolysis of the ester moiety in **VI** is effected by treatment with a hydroxide base, such as lithium hydroxide, to afford the corresponding acid **VII**. Treatment of the acid **VII** with 1,2-phenylenediamine in the presence of BOP reagent, triethylamine, and dimethylformamide (DMF) yields the anilinyl amide **VIII**.

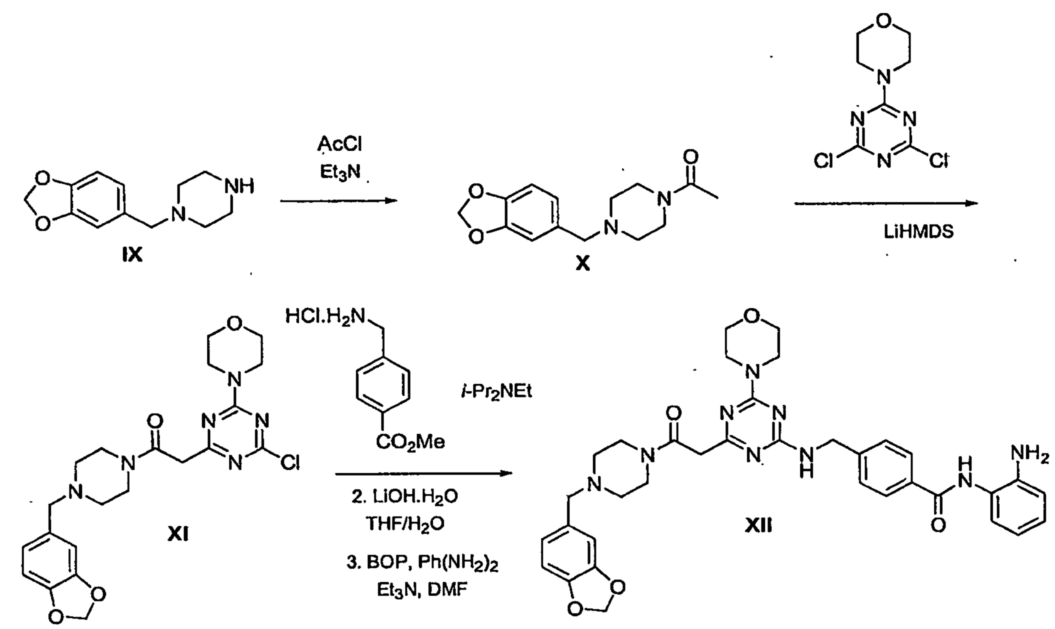
Scheme 1



[0105] Compounds of formula (1), wherein Y^1 is $-CH_2-C(O)-N(R^1)(R^2)$, preferably may be prepared as outlined in Scheme 2. Thus, piperazine

IX is treated with acetyl chloride and triethylamine to produce amide **X**. Reaction of **X** with dichloromorpholyltriazine and lithium hexamethyldisiloxane affords compound **XI**. The chloride of **XI** is converted to the anilinyl amide of **XII** as described above with respect to Scheme 1: treatment with the amine and diisopropylethylamine; followed by lithium hydroxide; followed by BOP reagent, phenylenediamine, triethylamine, and DMF.

Scheme 2

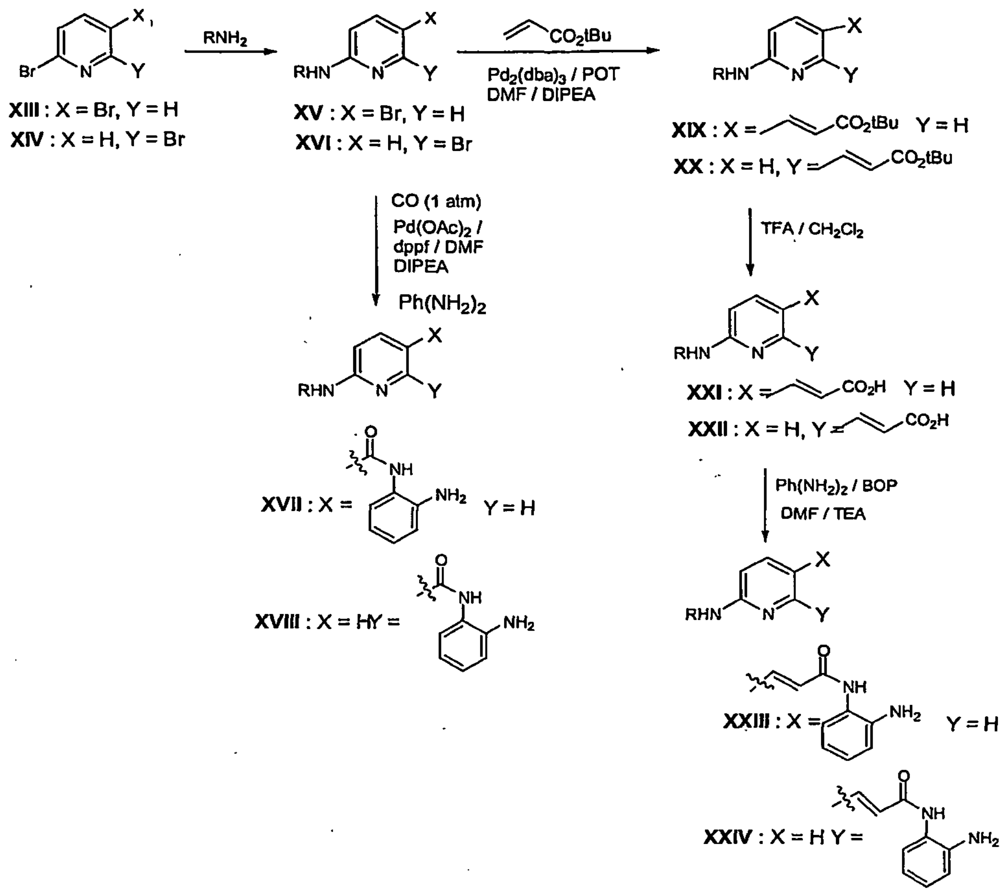


[0106] Compounds of formula (2), wherein Ar^2 is pyridylene and X^1 comprises $-N(R^7)-$, compounds of formula (3), wherein Ar^3 is pyridylene and X^2 comprises $-N(R^9)-$, and compounds of formula (4), wherein Ar^4 is pyridylene and X^3 comprises $-N(R^{11})-$, preferably may be prepared according to the procedures illustrated in Scheme 3. Dibromopyridine **XIII** or **XIV** is treated with amine RNH_2 to produce aminobromopyridine **XV** or **XVI**, respectively. Treatment of **XV** or **XVI** with diacetoxypalladium, diphenylphosphinoferrocene, DMF, diisopropylethylamine, and phenylenediamine under carbon monoxide yields anilinyl amide **XVII** or **XVIII**, respectively.

[0107] Treatment of **XV** or **XVI** with tert-butylacrylate, diisopropylethylamine, dibenzylacetone palladium, and tri-o-tolylphosphine (POT) in DMF under nitrogen affords compounds **XIX** and **XX**, respectively. The ester moiety of **XIX** or **XX** is hydrolyzed to produce the corresponding acid moiety in **XXI** or **XXII**, respectively, by reaction with trifluoroacetic acid in dichloromethane. Treatment of

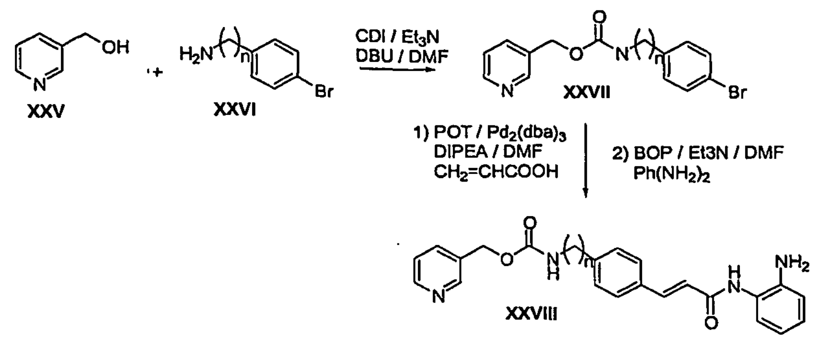
the acid **XXI** or **XXII** with phenylenediamine, BOP, and triethylamine affords the anilinyl amide **XXIII** or **XXIV**, respectively.

Scheme 3



[0108] Compounds of formula (2), wherein X^1 comprises -O-C(O)-NH-, preferably may be prepared according to the synthetic route depicted in Scheme 4. Thus, carbinol **XXV** is added to bromobenzylamine **XXVI** with carbonyldiimidazole (CDI), triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF to produce compound **XXVII**. The remaining synthetic steps in the production of anilinyl amide **XXVIII** are as described above for Scheme 3.

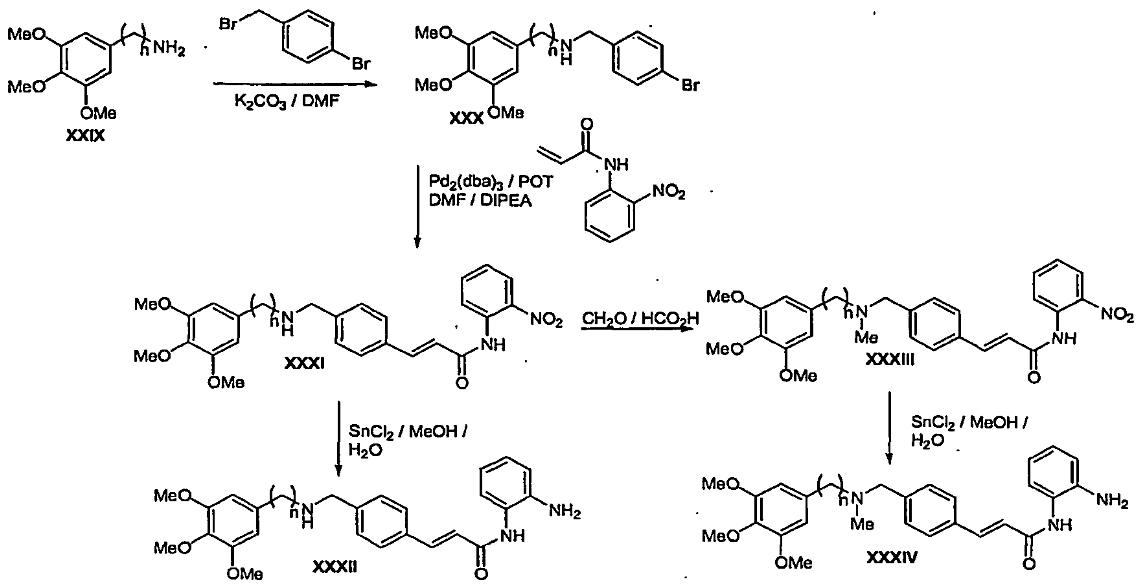
Scheme 4



[0109] Compounds of formula (2), wherein X^1 comprises $-N(R^7)-$, preferably may be prepared as outlined in Scheme 5. Amine XXIX is reacted with p-bromobenzylbromide in the presence of potassium carbonate in DMF to produce bromobenzylamine XXX. Treatment of XXX with nitroacrylanilide, dibenzylacetone palladium, POT, anddiisopropylethylamine in DMF affords nitroanilide XXXI. Nitroanilide XXXI is converted to the corresponding anilinyl amide XXXII by treatment with stannous chloride in methanol and water.

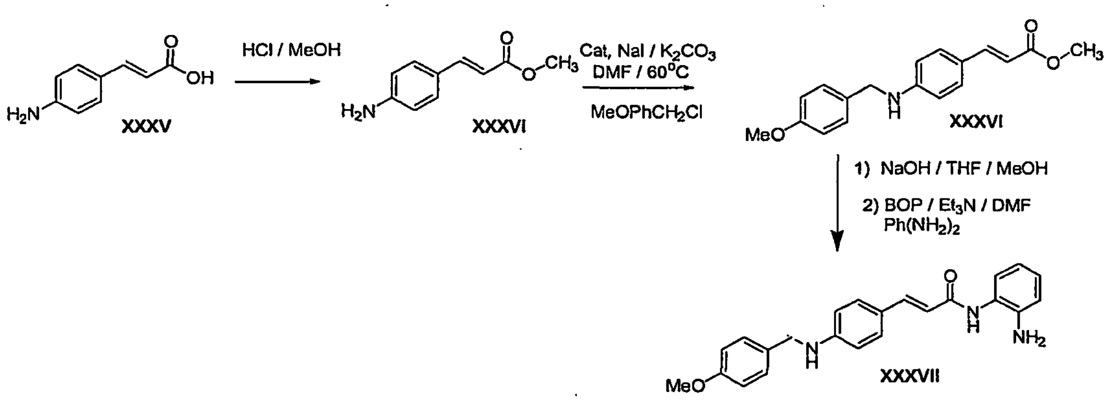
[0110] Treatment of amine **XXXI** in formic acid with paraformaldehyde provides methylamine **XXXIII**. The nitroanilide moiety in **XXXIII** is then converted to the corresponding anilinyl amide moiety in **XXXIV** by treatment with stannous chloride in methanol and water.

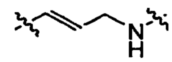
Scheme 5



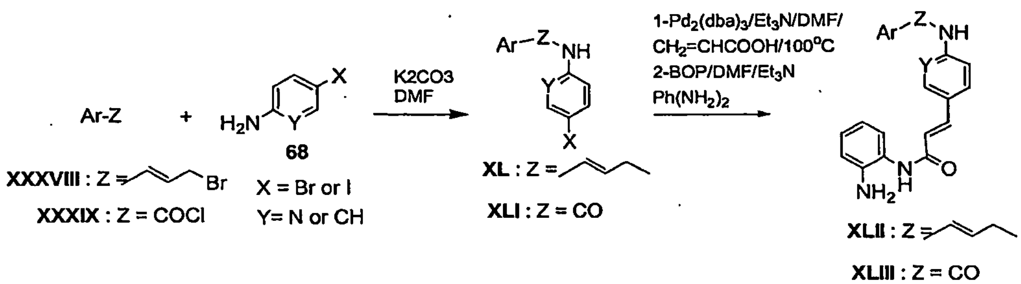
[0111] Alternatively, compounds of formula (2), wherein X^1 comprises $-N(R^7)-$, may be prepared according to the synthetic route depicted in Scheme 6. Carboxylic acid **XXXV** in methanol is treated with hydrochloric acid to produce ester **XXXVI**. Conversion of the primary amine moiety in **XXXVI** to the secondary amine moiety in **XXXVI** is effected by treatment with a catalyst such as triethylamine, methoxybenzylchloride, sodium iodide, and potassium carbonate in DMF at 60 °C. Ester **XXXVI** is converted to anilinyl amide **XXXVII** by treatment with sodium hydroxide, THF, and methanol, followed by BOP, triethylamine, and phenylenediamine in DMF, as described above for Scheme 3.

Scheme 6



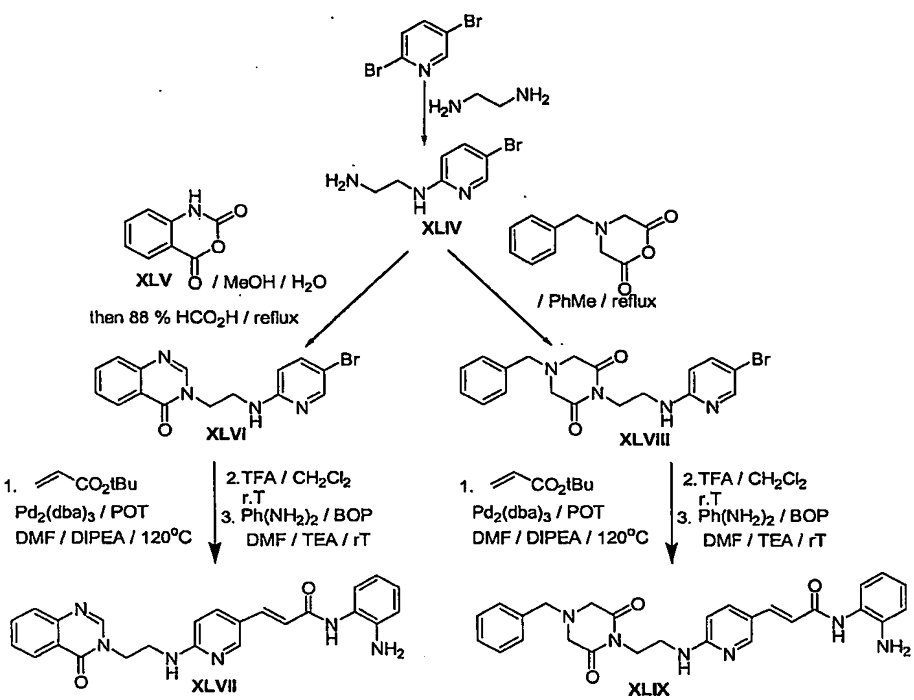
[0112] Compounds of formula (2), wherein X^1 comprises  or -C(O)-NH-, preferably may be prepared according to the procedures illustrated in Scheme 7. Addition of amine **68** to haloaryl compound **XXXVIII** or **XXXIX** and potassium carbonate in DMF provides arylamine **XL** or **XLI**, respectively. Anilinyl amide **XLII** or **XLIII** is then prepared using procedures analogous to those set forth in Schemes 3-6 above.

Scheme 7



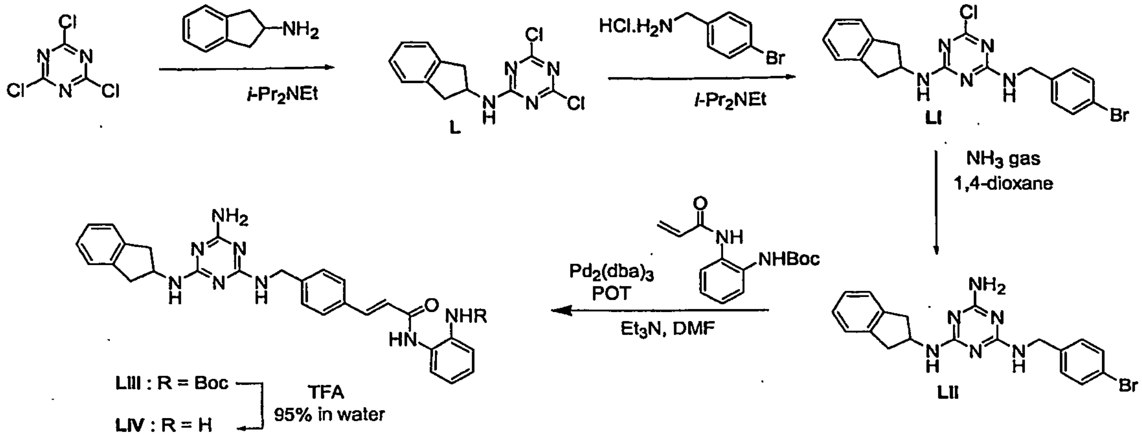
[0113] Compounds such as **XLVII** and **XLIX** preferably may be prepared as outlined in Scheme 8. Dibromopyridine is combined with diaminoethane to produce amine **XLIV**. Treatment of amine **XLIV** with isatoic anhydride **LV** in methanol and water, followed by refluxing in formic acid affords compound **XLVI**. Treatment of amine **XLIV** with the reaction products of benzylaminodiacetic acid and acetic anhydride provides compound **XLVIII**. Bromopyridylamines **XLVI** and **XLVIII** are then converted to the corresponding diene anilinylamides **XLVII** and **XLIX**, respectively, by procedures analogous to those set forth in Schemes 3-7 above.

Scheme 8



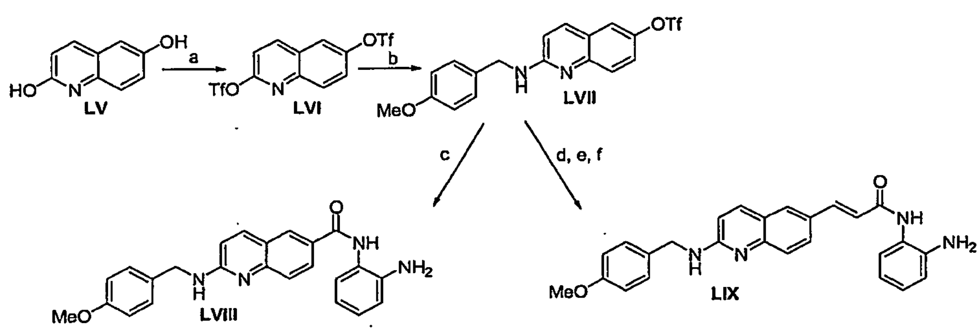
[0114] Compounds such as **LIV** preferably may be prepared according to the synthetic route depicted in Scheme 9. Trichlorotriazine is treated with aminoindan and diisopropylethylamine to produce dichloroaminotriazine **L**. Treatment with bromobenzylamine and diisopropylethylamine affords diaminochlorotriazine **LI**. Addition of ammonia gas and dioxane provides triaminotriazine **LII**. Treatment with protected acrylanilide, triethylamine, POT, and dibenzylacetone palladium then yields diene anilinylamide **LIII**, which is deprotected with trifluoroacetic acid to provide the final product **LIV**.

Scheme 9



[0115] Compounds of formula (2), wherein Ar^2 is quinolylene and X^1 comprises $-N(R^7)-$, compounds of formula (3), wherein Ar^3 is quinolylene and X^2 comprises $-N(R^9)-$, and compounds of formula (4), wherein Ar^4 is quinolylene and X^3 comprises $-N(R^{11})-$, preferably may be prepared according to the procedures illustrated in Scheme 10. Dihydroxyquinoline LV with dimethylaminopyridine (DMAP) in pyridine is treated with trifluoromethanesulfonic anhydride to provide bis(trifluoromethanesulfonyloxy)-quinoline LVI. Treatment of LVI with p-methoxybenzylamine affords aminoquinoline LVII. Anilinyl amides LVIII and LIX are then prepared using procedures analogous to those described for Schemes 1-9 above.

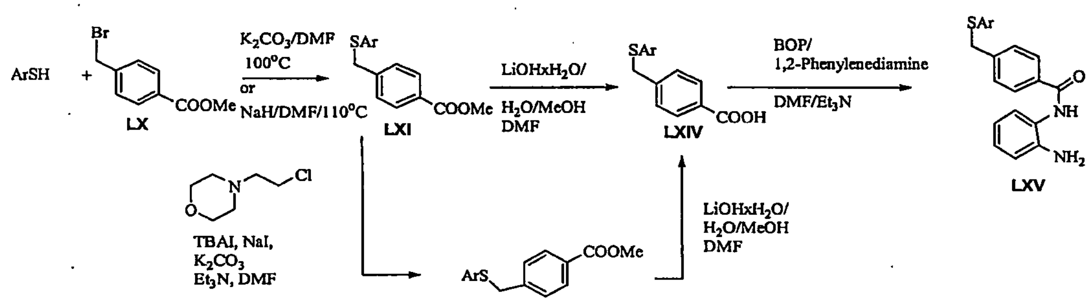
Scheme 10



a. Tf_2O / Py / DMAP / 0 C
b. p-methoxybenzylamine / 120 C
c. 1,2-phenylenediamine / CO (40 psi) / $Pd(OAc)_2$ / dppf / DMF / DIPEA / 70 C
d. t Butylacrylate / $Pd_2(dba)_3$ / POT / DMF / DIPEA / 120 C
e. TFA / DCM / rT
f. 1,2-phenylenediamine / BOP / DMF / TEA / rT

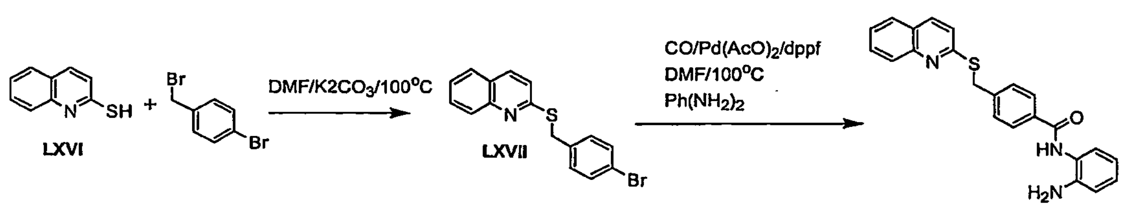
[0116] Compounds of formula (3), wherein X^2 comprises a sulfur atom, and compounds of formula (4), wherein X^3 comprises a sulfur atom, preferably may be prepared as outlined in Scheme 11. Bromide **LX** is converted to diaryl ester **LXI** using procedures analogous to those described for Scheme 6 above. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester **LXI** to the corresponding acid **LXIV**. Alternatively, ester **LXI** may be treated with chloroethylmorphonline, sodium iodide, potassium carbonate, triethylamine, and tetrabutylammonium iodide (TBAI) in DMF to produce ester **LXIII**, which is then converted to acid **LXIV** as in Scheme 1. Conversion of the acid **LXIV** to the anilinyl amide **LXV** is effected by procedures analogous to those set forth in Scheme 1 above.

Scheme 11



[0117] Alternatively, compounds of formula (3), wherein X^2 comprises a sulfur atom, and compounds of formula (4), wherein X^3 comprises a sulfur atom, may be prepared according to the procedures illustrated in Scheme 12. Sulfanyl anilinylamide LXVIII is prepared using procedures analogous to those set forth in Schemes 3 and 5 above.

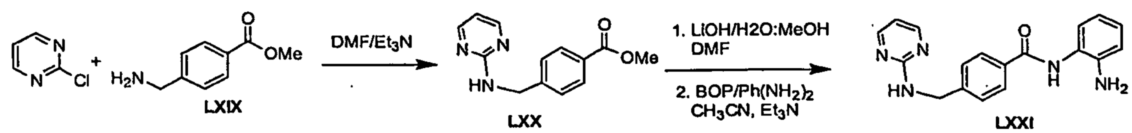
Scheme 12



[0118] Compounds of formula (3), wherein X^2 comprises $-N(R^9)-$, and compounds of formula (4), wherein X^3 comprises $-N(R^{11})-$, preferably may be

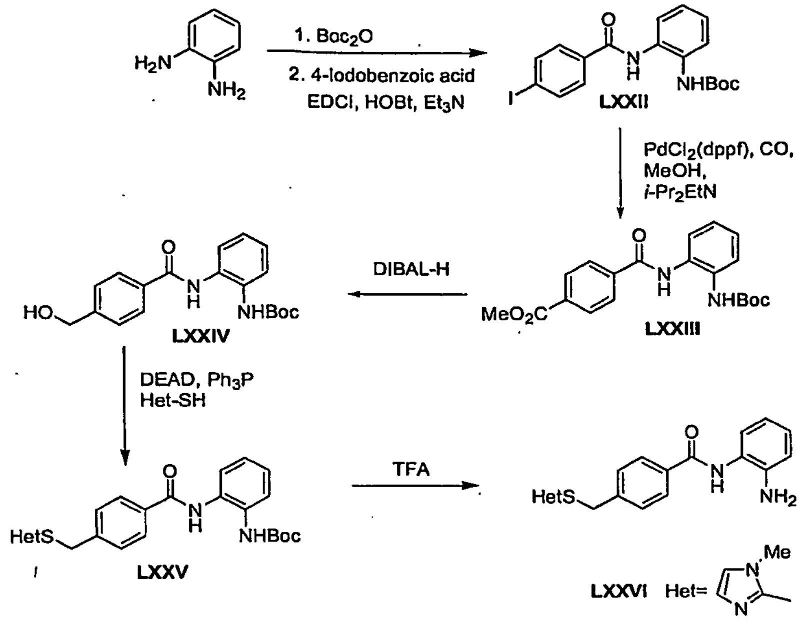
prepared according to the synthetic route depicted in Scheme 13. Amino anilinyl amide **LXXI** is prepared according to synthetic steps similar to those described for Schemes 1 and 6 above.

Scheme 13



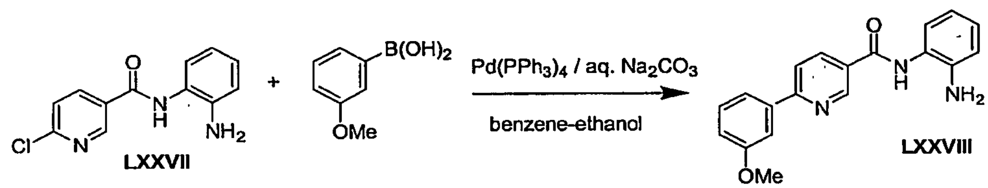
[0119] Compounds of formula (3), wherein X^2 comprises a sulfur atom, and compounds of formula (4), wherein X^3 comprises a sulfur atom, preferably may be prepared as outlined in Scheme 14. Phenylenediamine is reacted with di-tert-butyldicarbonate, followed by iodobenzoic acid, dimethylaminopropylethylcarbodiimide, hydroxybenzotriazole, and triethylamine to provide protected anilinyl amide **LXXII**. The iodide moiety of **LXXII** is converted to the methyl ester moiety of **LXXIII** using procedures analogous to those set forth for Scheme 3 above. The methyl ester moiety of **LXXIII** is converted to the hydroxyl moiety of **LXXIV** by treatment with a reducing agent such as diisobutylaluminum hydride (DIBAL-H). Addition of the heterocyclylsulfhydryl compound Het-SH with triphenylphosphine and diethylazodicarboxylate converts the hydroxyl moiety of **LXXIV** to the sulfanyl moiety of **LXXV**. **LXXV** is deprotected with trifluoroacetic acid to afford the sulfanyl anilinyl amide **LXXVI**.

Scheme 14



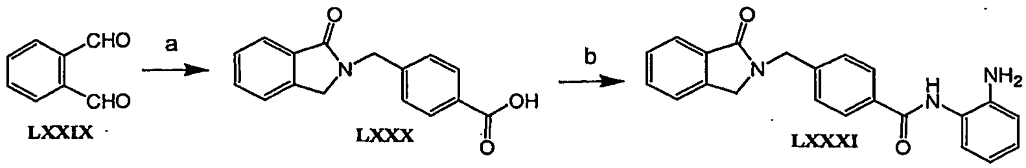
[0120] Compounds of formula (3), wherein X^2 is a chemical bond, preferably may be prepared according to the synthetic route depicted in Scheme 15. Thus, chloroarylanilinylamide **LXXVII** is treated with aryl boronic acid, benzene, ethanol, aqueous sodium carbonate, and triphenylphosphine palladium to afford the diarylanilinylamide **LXXVIII**.

Scheme 15



[0121] Compounds such as **LXXXI** preferably may be prepared according to the procedues illustrated in Scheme 16. Thus, benzene-1,2-carbaldehyde **LXXIX** in acetic acid is treated with p-aminomethylbenzoic acid to produce the benzoic acid **LXXX**. The acid **LXXX** is converted to the corresponding anilinylamide **LXXXI** by treatment with hydroxybenzotriazole, ethylenedichloride, and phenylenediamine.

Scheme 16

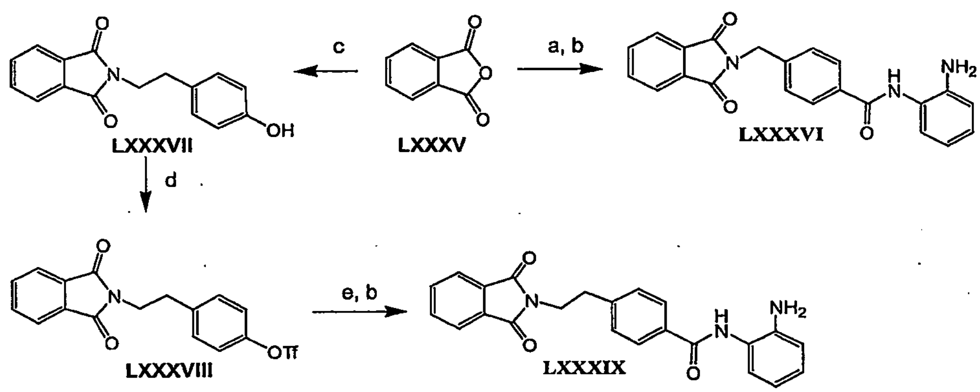


a. p-aminomethylbenzoic acid/AcOH/5 min/reflux
b. HOBT/EDC/1,2-diamino benzene

[0122] Compounds such as **LXXXVI** and **LXXXIX** preferably may be prepared according to the procedures illustrated in Scheme 18. Phthalic anhydride **LXXXV** and p-aminomethylbenzoic acid are combined in acetic acid to produce an intermediate carboxylic acid, which is converted to the anilinylamide **LXXXVI** using procedures analogous to those set forth in Schemes 15 and 16 above.

[0123] The addition of 4-(2-aminoethyl)phenol to phthalic anhydride **LXXXV** in acetic acid affords the hydroxyl compound **LXXXVII**. The hydroxyl group of **LXXXVII** is converted to the triflate group of **LXXXVIII** by treatment with sodium hydride, THF, DMF, and phenylaminoditriflate. Treatment of **LXXXVIII** according to procedures analogous to those described for Scheme 3 above affords the anilinylamide **LXXXIX**.

Scheme 18



a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs
b. HOBT/EDC/1,2-diamino benzene
c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux
d. $PhNTf_2$/NaH/THF-DMF/30 min/0^{o}C
e. 1. CO/$Pd(OAc)_2$/dppf/Et_3N/MeOH-DMF/4 days/75^{o}C
2. AcOH/HCl/3 hrs/reflux

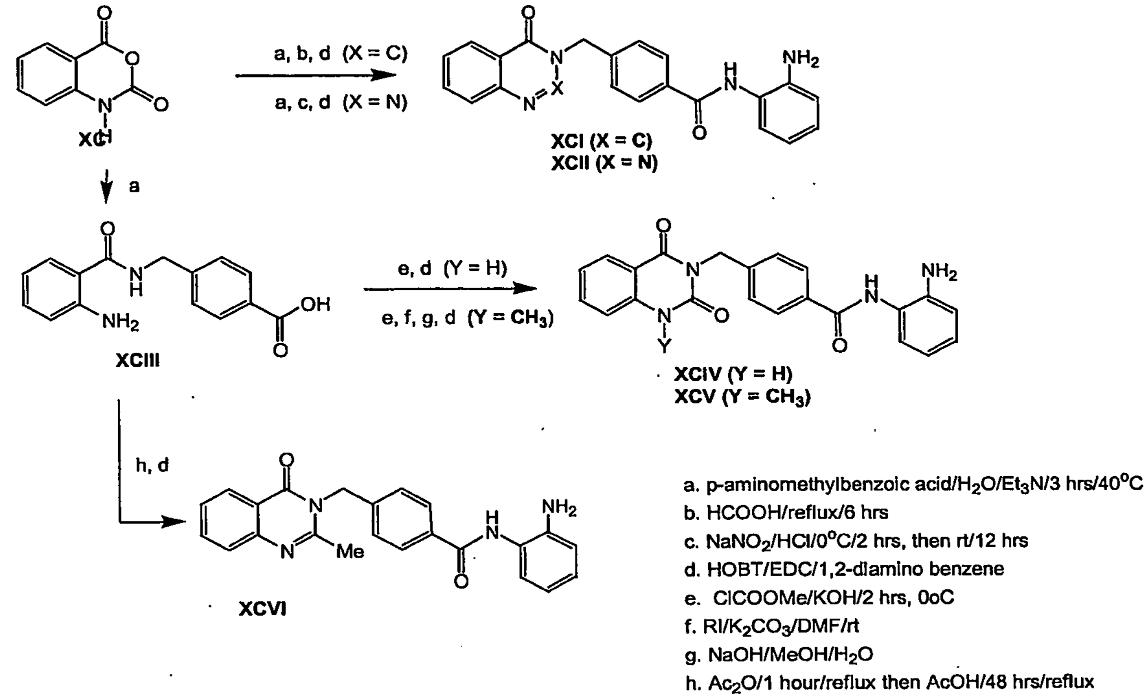
[0124] Compounds such as **XCI-XCVI** preferably may be prepared according to the synthetic route depicted in Scheme 19. Treatment of isatoic anhydride **XC** with p-aminomethylbenzoic acid in water and triethylamine, followed by formic acid affords an intermediate carboxylic acid, which is converted to anilinylamide **XCI** using procedures analogous to those described for Scheme 16 above.

[0125] Alternatively, treatment of isatoic acid **XC** with p-aminomethylbenzoic acid in water and triethylamine, follwed by hydrochloric acid and sodium nitrite affords an intermediate carboxylic acid, which is converted to anilinylamide **XCII** using procedures analogous to those described for Scheme 16 above.

[0126] Alternatively, treatment of isatoic acid **XC** with p-aminomethylbenzoic acid in water and triethylamine affords benzoic acid **XCIII**. Treatment of **XCIII** with sodium hydroxide, dioxane, methylchloroformate, and methanol affords an intermediate quinazolinedione carboxylic acid, the acid moiety of which is then converted to the anilinylamide moiety of **XCIV** using procedures analogous to those described for Scheme 16 above. Alternatively, the intermediate quanzolinedione carboxylic acid in DMF is treated with potassium carbonate and methyl iodide to produce an intermediate benzoic acid methyl ester, which is converted to an intermediate benzoic acid by treatment with sodium hydroxide, methanol, and water. The benzoic acid is then converted to the corresponding anilinylamide **XCV** using procedures analogous to those described for Scheme 16 above.

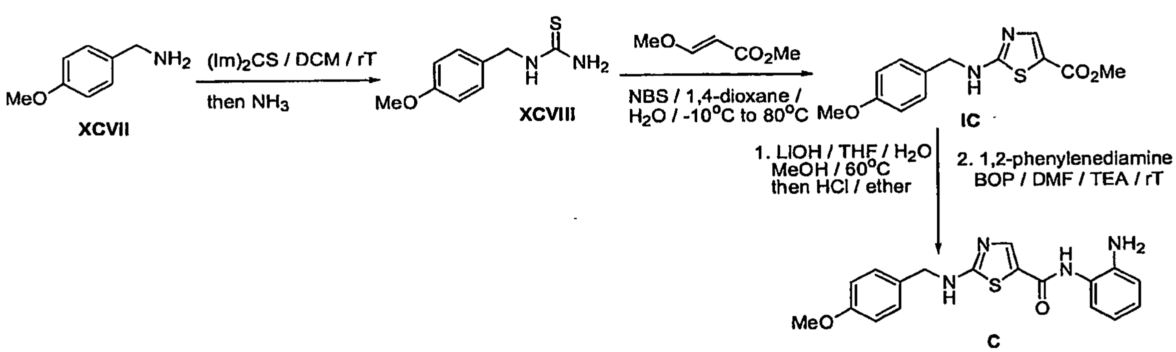
[0127] Alternatively, treatment of **XCIII** with acetic anhydride followed by acetic acid produces an intermediate carboxylic acid, which is converted to anilinylamide **XCVI** using procedures analogous to those described for Scheme 16 above.

Scheme 19



[0128] Compounds such as **C** preferably may be prepared as outlined in Scheme 20. Alkylamine **XCVII** is treated with thiocarbonyl diimidazole in dichloromethane, follwed by ammonium hydroxide to afford thiourea **XCVIII**. Treatment of thiourea **XCVIII** with methylmethoxyacrylate in dioxane and N-bromosuccinimide produces thiazole ester **IC**. The ester **IC** is converted to the corresponding anilinylamine **C** using procedures analogous to those set forth in Scheme 1 above.

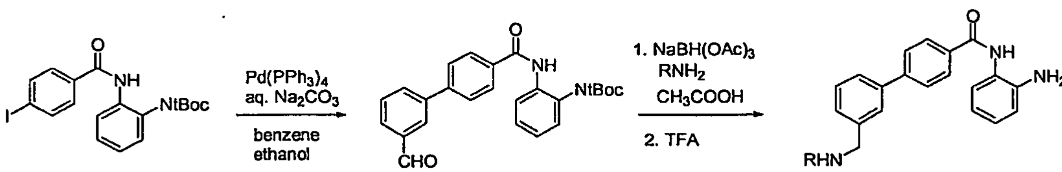
Scheme 20



[0129] Compounds of formula (3), wherein X^2 is a chemical bond and Cy^3 has an amino substituent preferably may be prepared according to the

synthetic route depicted in Scheme 21. Thus, protected iodoarylanilinylamide CI is treated according to procedures analogous to those described for Scheme 15 above afford the diarylanilinylamide CII. The aldehyde moiety in CII is converted to the corresponding secondary amine moiety by treatment with the primary amine and sodium triacetoxyborohydride followed by glacial acetic acid. The resultant compound is deprotected to yield CIII using procedures analogous to those set forth in Scheme 3 above.

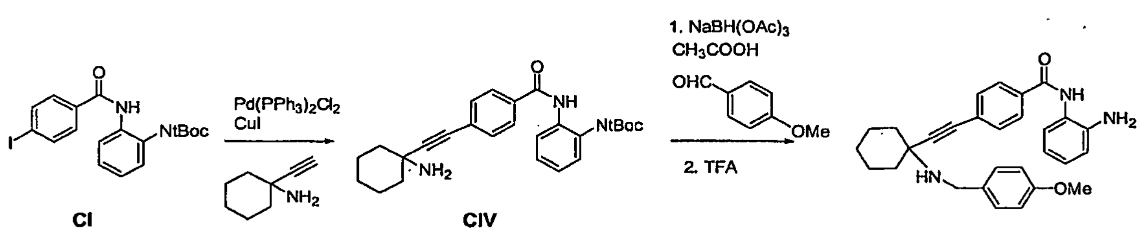
Scheme 21



CI CII CIII

[0130] Compounds of formula (3), wherein X^2 comprises an alkynylene moiety, and compounds of formula (4), wherein X^3 comprises an alkynylene moiety, preferably may be prepared as outlined in Scheme 22. Treatment of protected iodoarylanilinylamide CI with triphenylphosphine palladium chloride, cuprous iodide, and 1-ethynylcyclohexylamine affords the alkynylarylanilinylamide CIV. The primary amine moiety in CIV is converted to the corresponding secondary amine and the aniline moiety is deprotected to afford CV using procedures analogous to those described for Scheme 21 above.

Scheme 22



CI CIV CV

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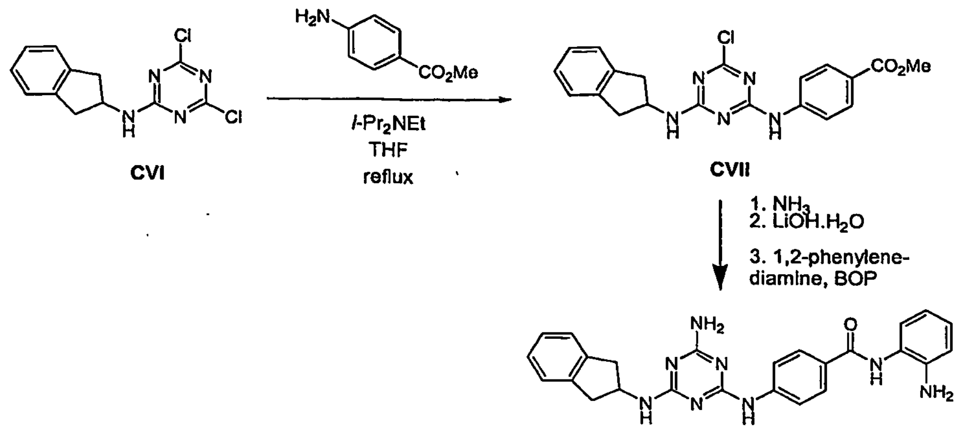
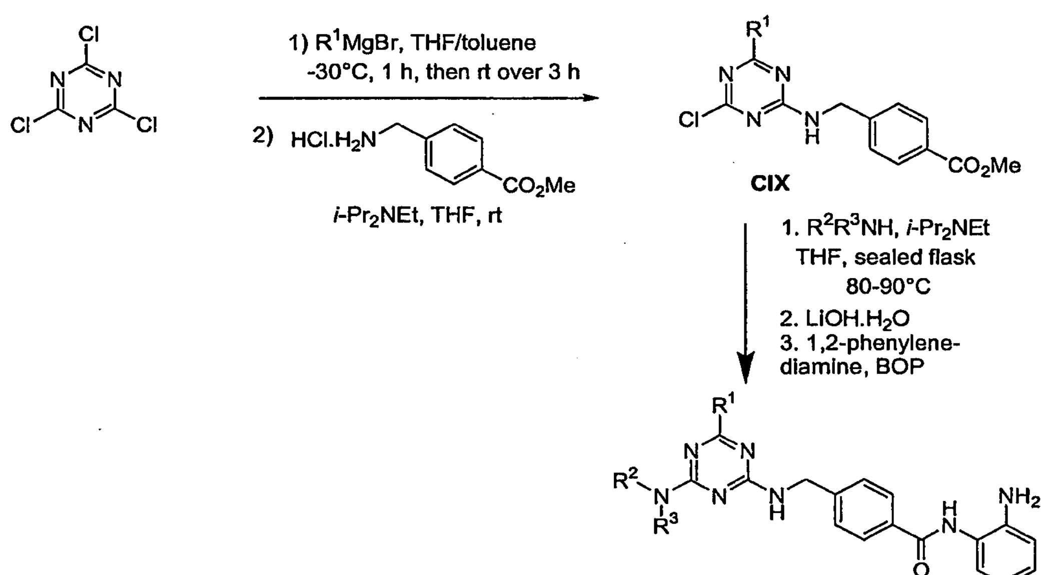
Scheme 24



CVIII

[0131] Compounds such as **CVIII** preferably may be prepared according to the synthetic route depicted in Scheme 24. Dichloroaminotriazine **CVI** is treated with methyl-4-aminobenzoate in the presence of diisopropylethylamine to produce diaminotriazine **CVII**. Addition of ammonia gas and dioxane, followed by a saponification and a peptide coupling using the same procedures analogous to those described for Scheme 1 above.

Scheme 30

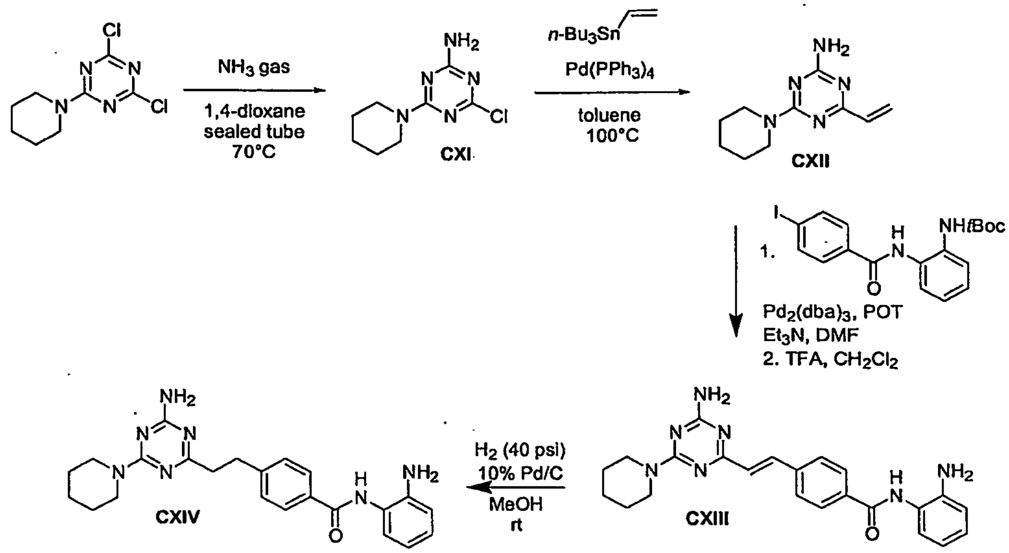


CX

[0132] Compounds such as **CX** preferably may be prepared according to the synthetic route depicted in Scheme 30. The Grignard reaction of

trichloroaminotriazine with various alkyl magnesium bromide, followed by a treatment with methyl-4-aminobenzoate in the presence of diisopropylethylamine yields alkylaminotriazine **CIX**. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester **CIX** to the corresponding anilinyl amide **CX**.

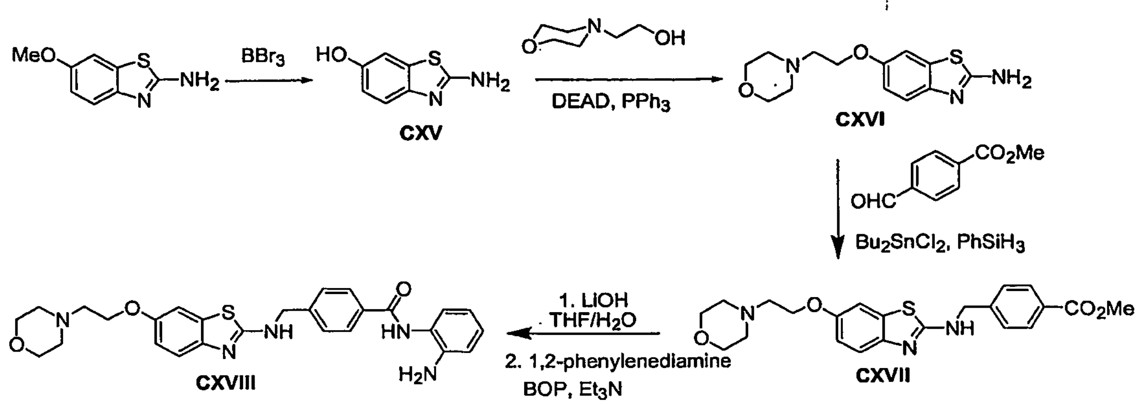
Scheme 32



[0133] Amination of dichlorotriazine proceeded using the usual condition described in Scheme 1 to afford **CXI**. Stille coupling using vinyl stannane provides **CXII**. Treatment with protected iodoanilide, triethylamine, POT and dibenzylacetone palladium then yields anilinylamide, which is deprotected with trifluoroacetic acid to provide the alkene **CXIII**. Hydrogenation of the alkene affords the final compound **CXIV**.

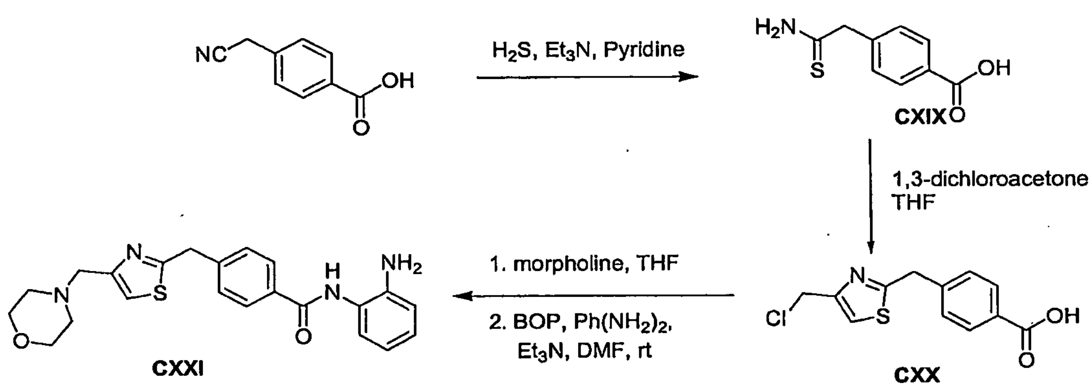
SUBSTITUTE SHEET (RULE 26)

Scheme 33



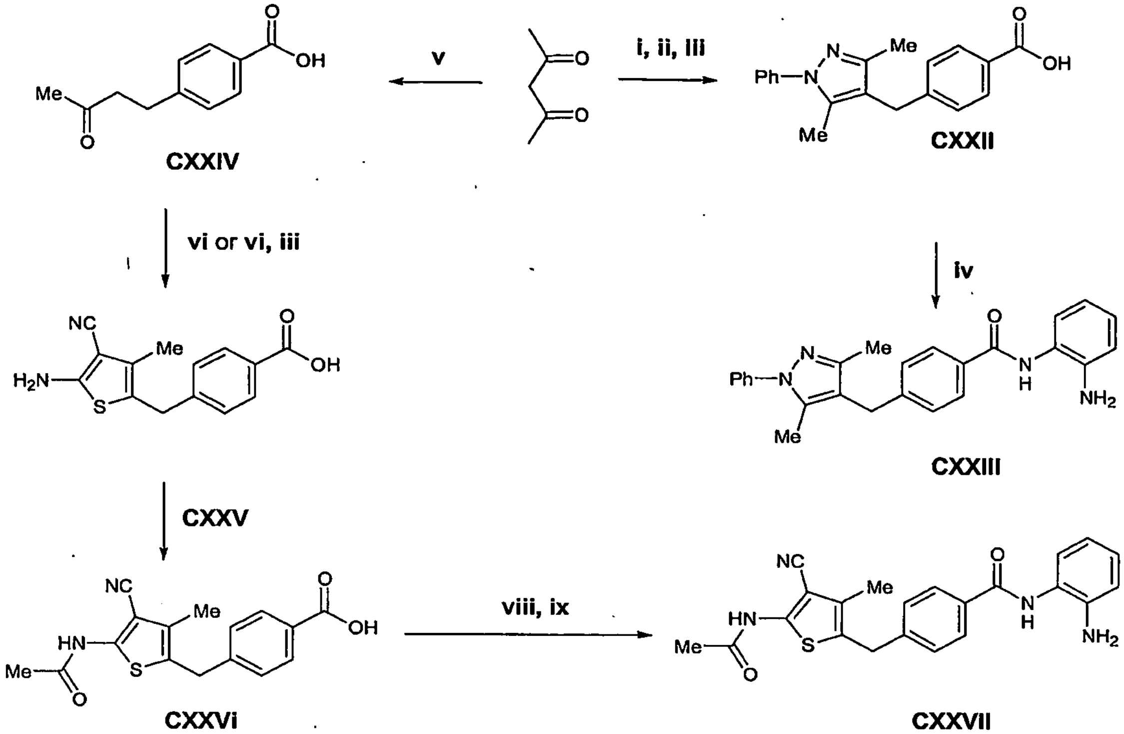
[0134] Compounds such as **CXVIII** preferably may be prepared according to the synthetic route depicted in Scheme 33. Treatment of methoxyaminobenzothiazole with tribromide boron affords the corresponding acid **CXV**. Mitsunobu reaction using hydroxyethyl morpholine in the presence of diethylazodicarboxylate and triphenylphosphine yields the amine **CXVI**. Reductive amination with methyl-4-formylbenzoate using phenylsilane and tin catalyst yields to the ester **CXVII**. Saponification followed by the usual peptide coupling analogous to those describe for Scheme 1 above provides the desired anilide **CXVIII**.

Scheme 42



[0135] Treatment 4-methylcyanobenzoic acid with hydrogen sulfide affords **CXIX**, which is subjected to cyclization in the presence of 1,3-dichloroacetone to yield **CXX**. Treatment with morpholine followed by a peptide coupling using the standard condition produces **CXXI**.

Scheme 49

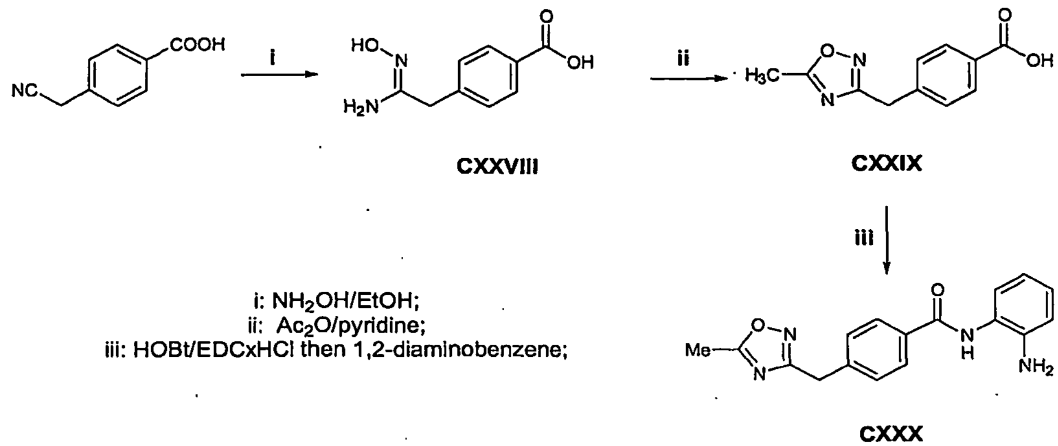


i: $BrCH_2C_6H_4COOMe/MeONa/THF$;
ii: $PhNHNH_2$;
iii: NaOH, then HCl
iv: HOBt/EDCxHCl then 1,2-diaminobenzene;
v: $BrCH_2C_6H_4COOMe/MeONa/MeOH$, then HCl/AcOH;
vi: $CH_2(CN)_2/S_8/Et_2NH$;
vii: AcCl;
viii: 2-N-Bocamino aniline;
ix: TFA;

[0136] Compounds such as **CXXIII** and **CXXVII** preferably may be prepared according to the synthetic scheme 49. Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and phenyl hydrazine followed by saponification, afforded the intermediate acid **CXXII**. This material was coupled with 1,2-diaminobenzene in a standard fashion to afford **CXXIII**.

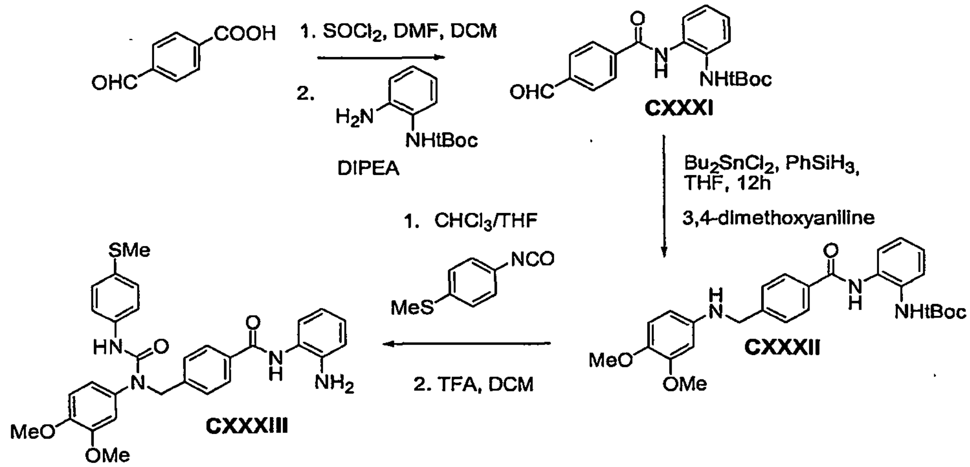
[0137] Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and a 1:1 mixture AcOH-HCl (conc.) afforded the intermediate acid **CXXIV**. This keto-acid reacting with sulfur and malonodinitrile in the presence of a base, produced the thiophene **CXXV**, which was converted into the desired **CXXVII** using standard procedures.

Scheme 50



[0138] Compounds such as CXXX preferably may be prepared according to the synthetic scheme 50. Treatment of 4-cyanomethylbenzoic acid with hydroxylamine produced the amidoxime CXXVIII, which upon treatment with acetic anhydride was converted into the oxadiazole CXXIX. The latter was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXX.

Scheme 57



[0139] Compounds such as CXXXIII preferably may be prepared according to the synthetic route depicted in Scheme 57. Treatment of 4-formylbenzoic acid with thionyl chloride afford the acyl chloride which is coupled with protected anilide to produce CXXXI. Reductive amination with dimethoxyaniline using phenylsilane and tin catalyst yields to the protected anilide CXXXII. Treatment with isocyanate followed by

deprotection with trifluoroacetic acid provides the ureidoanilide CXXXIII.

Pharmaceutical Compositions

[0140] In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0141] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

[0142] As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid,

and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

[0143] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

Inhibition of Histone Deacetylase

[0144] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase according to the invention. Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study of the role of histone deacetylase in biological processes. In addition, the compounds of the invention selectively inhibit certain isoforms of HDAC.

[0145] Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For example, Yoshida et al., J. Biol. Chem., **265**: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated

histones in trichostatin A treated cells. Taunton et al., Science, **272**: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

[0146] In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with, and reduce the enzymatic activity of, a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase.

[0147] Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

[0148] Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (i.e., the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that

inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., to apoptose), or to undergo necrotic cell death.

[0149] The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown in vitro in the G1 or G2 phase of the cell cycle. Such synchronization allows, for example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.

[0150] In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

[0151] In some preferred embodiments, the contacted cell is in an animal. Thus, the invention provides a method for treating a cell

proliferative disease or condition in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

[0152] The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

[0153] It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also provides a method for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0154] The present invention further provides a method for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0155] The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0156] When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01 μM to about 100 μM, more preferably from about 0.05 μM to about 50 μM, still more preferably from about 0.1 μM to about 25 μM, and still yet more preferably from about 0.5 μM to about 25 μM. For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

[0157] In certain preferred embodiments of the third aspect of the invention, the method further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC7, and/or HDAC-8 (see e.g., GenBank Accession Number U50079 for HDAC-1, GenBank Accession

Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

[0158] For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

[0159] For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

[0160] Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

[0161] For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

[0162] For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Patent No. 5,652,355).

[0163] The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) Proc. Natl. Acad. Sci. USA 94: 684-689.

[0164] Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) Methods in Molec. Biol. 20: 465-496).

[0165] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table 1. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides of the nucleotide sequences shown in Table 1.

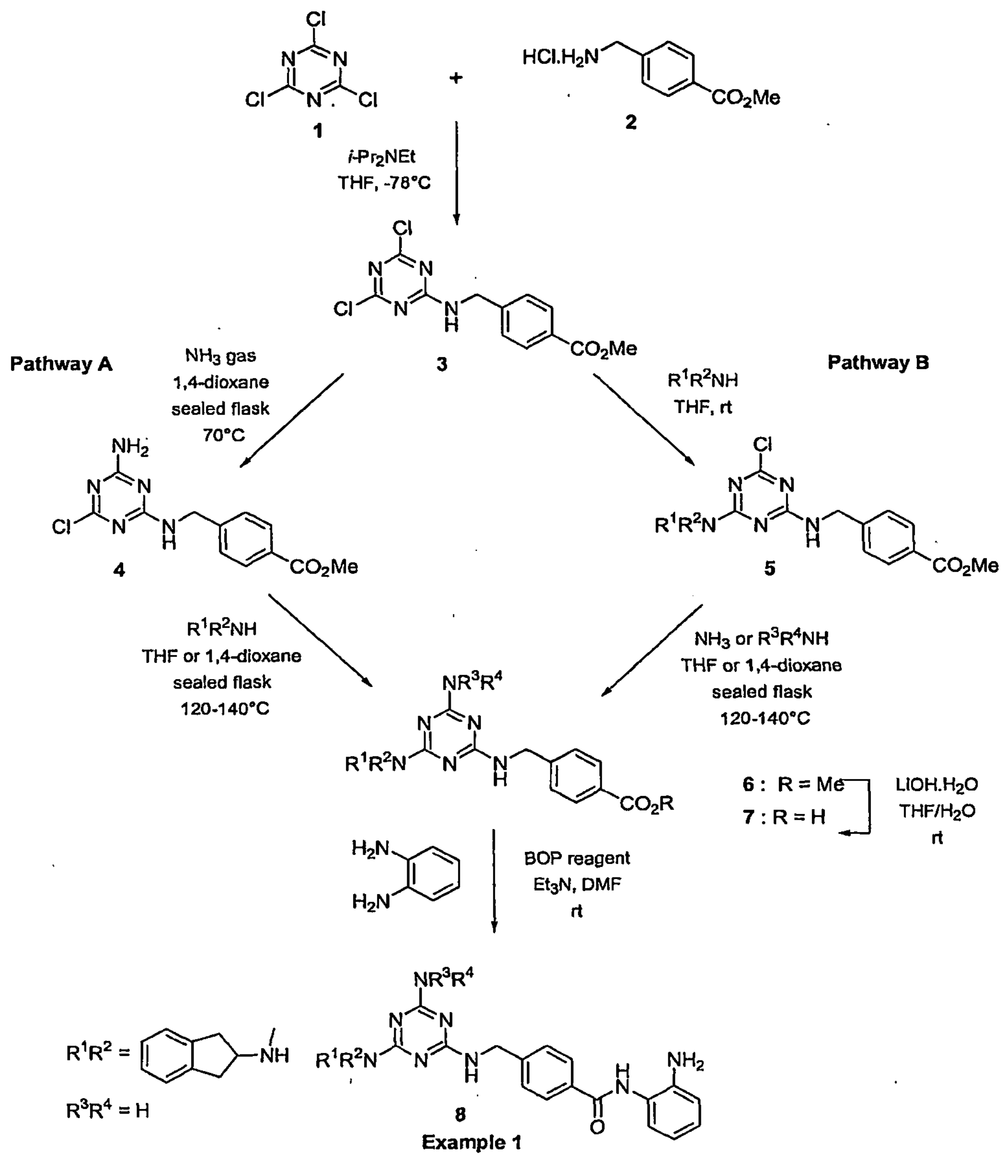
Table 1

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene
HDAC1 AS1	Human HDAC1	U50079	1585-1604	5'-GAAACGTGAGGGACTCAGCA-3'	3'-UTR
HDAC1 AS2	Human HDAC1	U50079	1565-1584	5'-GGAAGCCAGAGCTGGAGAGG-3'	3'-UTR
HDAC1 MM	Human HDAC1	U50079	1585-1604	5'-GTTAGGTGAGGCACTGAGGA-3'	3'-UTR
HDAC2 AS	Human HDAC2	U31814	1643-1622	5'-GCTGAGCTGTTCTGATTTGG-3'	3'-UTR
HDAC2 MM	Human HDAC2	U31814	1643-1622	5'-CGTGAGCACTTCTCATTTCC-3'	3'-UTR
HDAC3 AS	Human HDAC3	AF039703	1276-1295	5'-CGCTTTCCTTGTCATTGACA-3'	3'-UTR
HDAC3 MM	Human HDAC3	AF039703	1276-1295	5'-GCCTTTCCTACTCATTGTGT-3'	3'-UTR
HDAC4 AS1	Human HDAC4	AB006626	514-33	5-GCTGCCTGCCGTGCCCACCC-3'	5'-UTR
HDAC4 MM1	Human HDAC4	AB006626	514-33	5'-CGTGCCTGCGCTGCCCACGG-3'	5'-UTR
HDAC4 AS2	Human HDAC4	AB006626	7710-29	5'-TACAGTCCATGCAACCTCCA-3'	3'-UTR
HDAC4 MM4	Human HDAC4	AB006626	7710-29	5'-ATCAGTCCAACCAACCTCGT-3'	3'-UTR
HDAC5 AS	Human HDAC5	AF039691	2663-2682	5'-CTTCGGTCTCACCTGCTTGG-3'	3'-UTR
HDAC6 AS	Human HDAC6	AJ011972	3791-3810	5'-CAGGCTGGAATGAGCTACAG-3'	3'-UTR
HDAC6 MM	Human HDAC6	AJ011972	3791-3810	5'-GACGCTGCAATCAGGTAGAC-3'	3'-UTR
HDAC7 AS	Human HDAC7	AF239243	2896-2915	5'-CTTCAGCCAGGATGCCCACA-	3'-UTR

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene
				3′	
HDAC8 AS1	Human HDAC8	AF230097	51-70	5′-CTCCGGCTCCTCCATCTTCC-3′	5′-UTR
HDAC8 AS2	Human HDAC8	AF230097	1328-1347	5′-AGCCAGCTGCCACTTGATGC-3′	3′-UTR

[0166] The following examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

EXAMPLES



Example 1

4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (compound 8)

Step 1: Methyl-4-[(4,6-dichloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 3)

[0167] To a stirred solution at –78°C of cyanuric chloride **1** (8.23 g, 44.63 mmol) in anhydrous THF (100 mL) under nitrogen was added a suspension of methyl 4-(aminomethyl)benzoate.HCl **2** (10.00 g, 49.59 mmol), in anhydrous THF (50 mL), followed by i-Pr_2NEt (19.00 mL, 109.10 mmol). After 30 min, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 5/95) to afford the title compound **3** (12.12 g, 38.70 mmol, 87% yield) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): AB system (δ_A = 8.04, δ_B = 7.38, J = 8.5 Hz, 4H), 6.54 (bt, 1H), 4.76 (d, J = 6.3 Hz, 2H), 3.93 (s, 3H).

Pathway A

Step 2: Methyl-4-[(4-amino-6-chloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 4)

[0168] In a 150 mL sealed flask, a solution of **3** (6.00 g, 19.16 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH_3 gas for 5 min, and warmed to 70°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH_3 gas was repeated at room temperature for 5 min, and the reaction mixture was warmed to 70°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 30/70) to afford the title compound **4** (5.16 g, 17.57 mmol, 91% yield) as

a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): AB system (δ_A = 8.01, δ_B = 7.35, J = 8.1 Hz, 4H), 5.79 (bs, 1H), 5.40-5.20 (m, 2H), 4.72-4.63 (m, 2H), 3.91 (s, 3H).

Pathway B

Step 2: Methyl 4-[(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 5)

[0169] To a stirred solution at room temperature of **3** (3.00 g, 9.58 mmol) in anhydrous THF (50 mL) under nitrogen were added *i*-Pr_2NEt (8.34 mL, 47.90 mmol) and 2-aminoindan.HCl (1.95 g, 11.50 mmol) or R^1R^2NH (1.2 equiv), respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat*. NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound **5** (4.06 g, 9.91 mmol, quantitative yield) as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): mixture of rotamers, 8.06-7.94 (m, 2H), 7.43-7.28 (m, 2H), 7.24-7.12 (m, 4H), 6.41 and 6.05 (2 bt, 1H), 5.68-5.44 (m, 1H), 4.92-4.54 (m, 3H), 3.92 (bs, 3H), 3.41-3.12 (m, 2H), 2.90-2.70 (m, 2H).

Step 3: Methyl-4-[(4-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 6)

General procedure for the amination with NH_3 gas:

[0170] In a 150 mL sealed flask, a solution of **5** (3.90 g, 9.51 mmol) in anhydrous 1,4-dioxane (80 mL) was stirred at room temperature, saturated with NH_3 gas for 5 min, and warmed to 140°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH_3 gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat*. NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 3/97) to afford the title compound **6** (3.50 g, 8.96 mmol, 94% yield) as a pale yellow sticky solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.99 (bd, J = 8.2 Hz, 2H),

7.41-7.33 (m, 2H), 7.24-7.13 (m, 4H), 5.50-5.00 (m, 2H), 4.90-4.55 (m, 5H), 3.92 (s, 3H), 3.40-3.10 (m, 2H), 2.90-2.70 (m, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$) δ (ppm): 166.88, 167.35, 166.07, 144.77, 141.07, 129.82, 128.93, 127.01, 126.61, 124.70, 52.06, 51.80, 44.25, 40.16. HRMS (calc.): 390.1804, (found): 390.1800.

Pathways A and B, step 3, general procedure with primary and/or secondary amines:

[0171] In a 50-75 mL sealed flask, a stirred solution of **4** (500 mg, 1.70 mmol, 1 equiv), *i*-Pr_2NEt (1.48 mL, 8.51 mmol, 5 equiv) and R^1R^2NH or R^3R^4NH (1.5-3 equiv) in anhydrous THF or 1,4-dioxane (20-30 mL) was warmed to 120-140°C for 15-24 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat*. NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel to afford the title compound.

Step 4: 4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (compound 7)

[0172] To a stirred solution at room temperature of **6** (2.07 g, 5.30mmol) in THF (50 mL) was added a solution of $LiOH.H_2O$ (334 mg, 7.96 mmol) in water (25 mL). After 18 h, the reaction mixture was diluted in water and acidified with 1 N HCl until pH 5-6 in order to get a white precipitate. After 1 h, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **7** (1.73 g, 4.60 mmol, 87% yield) as a white solid. ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 8.05 (bd, J = 8.1 Hz, 2H), 7.56-7.42 (m, 2H), 7.30-7.10 (m, 4H), 5.90-5.65 (m, 2H), 4.85-4.60 (m, 4H), 3.40-2.80 (m, 4H). HRMS (calc.): 376.1648, (found): 376.1651.

Step 5: 4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-*N*-(2-amino-phenyl)-benzamide (compound 8)

[0173] To a stirred solution at room temperature of **7** (200 mg, 0.53 mmol) in anhydrous DMF (5 mL) under nitrogen were added Et_3N (74 µl, 0.53 mmol) and BOP reagent (282 mg, 0.64 mmol), respectively. After 40 min, a solution of 1,2-phenylenediamine (64 mg, 0.58 mmol), Et_3N (222 µl, 1.59

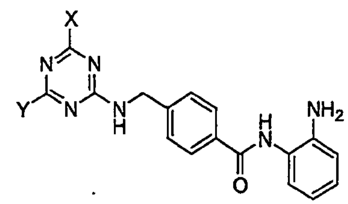
mmol) in anhydrous DMF (2 mL) was added dropwise. After 1.5 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 2/98→5/95) to afford the title compound **8** (155 mg, 0.33 mmol, 63% yield) as a pale yellow foam. ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 9.04 (bs, 1H), 7.96 (bd, J = 8.0 Hz, 2H), 7.50-7.40 (m, 2H), 7.30 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.22-7.08 (m, 4H), 6.99 (ddd, J = 8.0 Hz, 7.5 Hz, 1.5 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 7.5 Hz, 1.4 Hz, 1H), 6.60-5.49 (m, 4H), 4.80-4.50 (m, 4H), 3.30-3.08 (m, 2H), 2.96-2.74 (m, 2H).

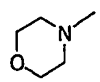
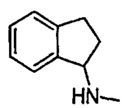
EXAMPLES 2-28

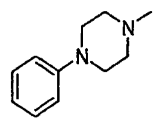
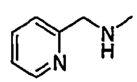
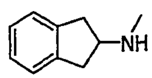
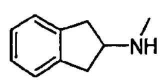
[0174] Examples 2 to 28 describe the preparation of compounds **9** to **35** using the same procedure as described for compound **8** of Example 1. Characterization data are presented in Tables 2a and 2b.

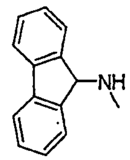
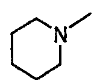
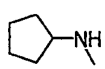
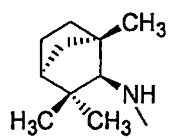
Table 2a

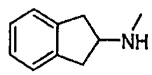
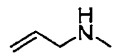
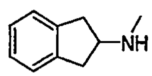
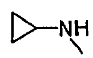
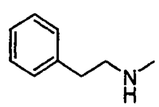
Characterization of Compounds Prepared in Examples 2-28

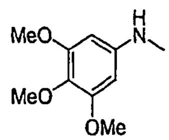
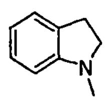
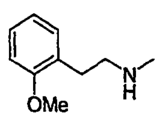
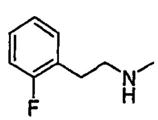


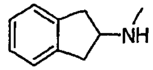
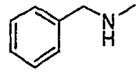
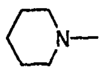
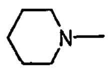
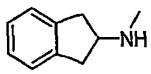
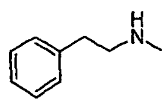
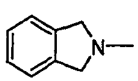
Ex.	Cpd	Y	X	Name	Characterization	Schm
2	9		NH_2	4-[(4-amino-6-morpholin-4-yl-[1,3,5]-triazin-2-ylamino)-methyl]-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR ($CDCl_3$)** δ (ppm): 8.02 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.31 (m, 1H), 7.08 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.82 (t, J = 6.7 Hz, 2H), 5.62 (t, J = 5.9 Hz, 1H), 4.90 (bs, 2H), 4.61 (d, J = 6.0 Hz, 2H), 3.75-3.62 (m, 10H).	1A
3	10		NH_2	4-{[4-amino-6-(1-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.07 (bs, 1H), 8.05-7.95 (m, 2H), 7.55-7.45 (m, 2H), 7.37-7.10 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.55 (m, 5H), 4.75-4.60 (m, 3H), 3.05-2.75 (m, 2H), 2.60-2.45 (m, 1H)), 2.00-1.84 (m, 1H). **HRMS** (calc.): 466.2229, (found): 466.2225	1A

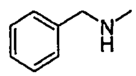
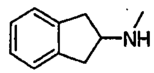
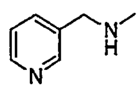
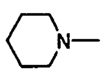
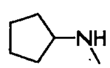
Ex.	Cpd	Y	X	Name	Characterization	Schm
4	11		NH_2	*N*-(2-Amino-phenyl)-4-{[4-amino-6-(4-phenyl-piperazin-1-yl)-[1,3,5]triazin-2-ylamino]-methyl}-benzamide	**^{1}H NMR (acetone-d$_6$)** δ (ppm): mixture of rotamers, 9.05-9.00 (m, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.93 (s), 7.84 (d, J = 8.0 Hz), 7.72 (d, J = 8.2 Hz), 7.58-7.40 (m, 3H), 7.31-7.19 (m, 3H), 7.12-7.05 (m), 6.98 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.80 (t, J = 7.1 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 6.57-6.50 (m, 1H), 5.78-5.60 (m, 2H), 4.67-4.64 (m, 2H), 3.88-3.84 (m, 4H), 3.14 (s, 4H). **HRMS** (calc.): 477.2389 [$M^{+\cdot}$ – NH_4], (found): 477.2383	1A
5	12		NH_2	4-{[4-amino-6-(2-pyridinyl-methyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d$_6$)** δ (ppm): 9.08 (bs, 1H), 8.51 (bs, 1H), 8.05-7.90 (m, 2H), 7.80-7.60 (m, 1H), 7.55-7.15 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85-6.55 (m, 1H), 5.84 (bs, 2H), 4.75-4.60 (m, 4H). **HRMS** (calc.): 441.2025, (found): 441.2029	1A
6	13			4-{[4,6-bis-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d$_6$)** δ (ppm): 9.08 (bs, 1H), 8.05-7.95 (m, 2H), 7.56-7.44 (m, 2H), 7.34 (bd, J = 7.7 Hz, 1H), 7.27-7.10 (m, 8H), 7.04 (td, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.90 (m, 3H), 4.90-4.58 (m, 6H), 3.40-2.80 (m, 4H). **HRMS** (calc.): 582.2855, (found): 582.2838	1B

Ex.	Cpd	Y	X	Name	Characterization	Schm
7	14		NH_2	4-{[4-Amino-6-(9*H*-fluoren-9-ylamino)-[1,3,5]triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.05-9.00 (m, 1H), 8.03-7.87 (m, 2H), 7.80-7.70 (m, 2H), 7.63-7.20 (m, 9H), 7.00 (t, 1H), 6.86 (d, 1H), 6.66 (t, 1H), 6.50-5.50 (m, 6H), 4.75-4.55 (m, 3H). **HRMS** (calc.): 514.2229, (found): 514.2232	1B
8	15		NH_2	N-(2-amino-phenyl)-4-[(4-amino-6-piperidin-1-yl-[1,3,5]-triazin-2-ylamino)-methyl]-benzamide	**^{1}H NMR ($CDCl_3$)** δ (ppm): 7.96 (bs, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.08 (dt, *J* = 7.7 Hz, 1.4 Hz, 1H), 6.83 (t, *J* = 6.6 Hz, 2H), 5.47 (bs, 1H), 4.80 (bs, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.88 (bs, 2H), 3.67 (t, *J* = 5.2 Hz, 4H), 1.66-1.58 (m, 2H,), 1.56-1.48 (m, 4H).	1A
9	16		NH_2	4-[(4-amino-6-cyclopentyl-amino-[1,3,5]-triazin-2-yl-amino) -methyl]-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR ($CDCl_3$)** δ (ppm): 7.97 (bs, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.39-7.34 (m, 3H), 7.10 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 6.85 (t, *J* = 7.0 Hz, 2H), 5.56 (bs, 1H), 4.90 (bs, 3H), 4.62 (s, 2H), 4.25-4.19 (m, 1H) 3.88 (bs, 2H), 1.95 (m, 2H), 1.71-1.59 (m, 4H), 1.43-1.37 (m, 2H).	1A
10	17		NH_2	(1*R*)-4-{[4-amino-6-(2-*exo*-fenchyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.08 (bs, 1H), AB system (δ_A = 8.00, δ_B = 7.51, *J* = 8.0 Hz, 4H), 7.33 (bd, *J* = 7.7 Hz, 1H), 7.03 (ddd, *J* = 8.0 Hz, 7.3 Hz, 1.4 Hz, 1H), 6.90 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 6.60-6.28 (m, 1H), 5.80-5.20 (m, 3H), 4.67 (bs, 4H), 3.87 (bd, *J* = 9.1 Hz, 1H), 1.80-1.60 (m, 4H), 1.56-1.42 (m, 1H), 1.34-1.00 (m including 2 s, 8H), 0.84 (s, 3H). **HRMS** (calc.): 486.2855, (found): 486.2844	1A

Ex.	Cpd	Y	X	Name	Characterization	Schm
11	18			4-{[4-allyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	[1]H **NMR (acetone-d_6)** δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.4 Hz, 2H), 7.58-7.42 (m, 2H), 7.34 (bd, J = 8.0 Hz, 1H), 7.27-7.10 (m, 4H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.60-5.70 (m, 3H), 5.26-5.00 (m, 2H), 4.86-4.54 (m, 4H), 4.10-3.90 (m, 2H), 3.38-3.10 (m, 2H), 3.00-2.80 (m, 2H). **HRMS** (calc.): 506.2542, (found): 506.2533	1B
12	19			4-{[4-cyclopropyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	[1]H **NMR (acetone-d_6)** δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.7 Hz, 2H), 7.60-7.40 (m, 2H), 7.33 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.28-7.10 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.3 Hz, 1H), 6.67-5.80 (m, 2H), 4.90-4.50 (m, 4H), 3.40-3.10 (m, 2H), 3.05-2.70 (m, 3H), 0.75-0.43 (m, 4H). **HRMS** (calc.): 506.2542, (found): 506.2548	1B
13	20		NH_2	4-[(4-Amino-6-phenethylamino-[1,3,5]triazin-2-ylamino)-methyl]-*N*-(2-amino-phenyl)-benzamide	[1]H **NMR (acetone-d_6)** δ (ppm): 9.03 (s, 1H), 7.97 (d, J = 7.7 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.99 (td, J = 8.0 Hz, 1.3 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.3 Hz, 1H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.62-5.40 (m, 5H), 4.75-4.45 (m, 3H), 3.59-3.45 (m, 2H), 2.95-2.70 (m, 2H). **HRMS** (calc.): 454.2229, (found): 454.2235	1A

Ex.	Cpd	Y	X	Name	Characterization	Schm
14	21		NH_2	*N*-(2-Amino-phenyl)-4-{[4-amino-6-(3,4,5-trimethoxy-phenylamino)-[1,3,5]triazin-2-ylamino]-methyl}-benzamide	**^{1}H NMR ($CDCl_3$/MeOD)** δ (ppm): 7.72 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.91 (td, *J* = 7.7 Hz, 1.2 Hz, 1H), 6.70-6.61 (m, 4H), 4.61 (bs, 2H), 3.58-3.52 (m, 9H).	1B
15	22		NH_2	4-{[4-Amino-6-(2,3-dihydro-indol-1-yl)-[1,3,5]triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR ($CDCl_3$/MeOD)** δ (ppm): 8.06 (bs, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.02-6.96 (m, 2H), 6.84-6.71 (m, 3H), 4.61 (bs, 2H), 4.03 (t, *J* = 8.5 Hz, 2H), 3.02 (t, *J* = 8.5 Hz, 2H).	1B
16	23		NH_2	4-({4-Amino-6-[2-(2-methoxy-phenyl)-ethylamino]-[1,3,5]triazin-2-ylamino}-methyl)-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): mixture of rotamers, 9.06 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.21-6.70 (m, 6H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.60-5.70 (m, 5H), 4.75-4.55 (m, 3H), 3.81 (s, 3H), 3.55-3.45 (m, 2H), 2.90-2.78 (m, 2H). **HRMS** (calc.): 484.2335, (found): 484.2331	1A
17	24		NH_2	4-({4-Amino-6-[2-(2-fluoro-phenyl)-ethylamino]-[1,3,5]triazin-2-ylamino}-methyl)-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): mixture of rotamers, 9.03 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.38-7.17 (m, 2H), 7.17-6.95 (m, 4H), 6.86 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.67 (t, *J* = 7.0 Hz, 1H), 6.50-5.60 (m, 5H), 4.75-4.55 (m, 3H), 3.60-3.52 (m, 2H), 2.95-2.85 (m, 2H). **HRMS** (calc.): 472.2135, (found): 472.2146	1A

Ex.	Cpd	Y	X	Name	Characterization	Schm
18	25			4-{[4-benzyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	^{1}H NMR **(acetone-d_6)** δ (ppm): 9.06 (bs, 1H), 8.04-7.93 (m, 2H), 7.57-7.12 (m, 12H), 7.04 (td, *J* = 7.6 Hz, 1.5 Hz, 1H), 6.91 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 6.72 (bt, *J* = 7.6 Hz, 1H), 6.68-5.90 (m, 3H), 4.84-4.50 (m, 7H), 3.35-3.13 (m, 2H), 3.00-2.80 (m, 2H). **HRMS** (calc.): 556.2699, (found): 556.2706	1B
19	26			*N*-(2-Amino-phenyl)-4-[(4,6-di-piperidin-1-yl-[1,3,5]triazin-2-ylamino)-methyl]-benzamide	^{1}H NMR: **($CDCl_3$)** δ (ppm): 7.83 (d, *J* = 8.2 Hz, 3H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, *J* = 6.2 Hz, 1H), 4.64 (d, *J* = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, *J* = 5.4 Hz, 8H), 1.63-1.53 (m, 12H).	1B
20	27			4-{[6-(2-indanyl-amino)-4-phenethyl-amino-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	^{1}H NMR **(acetone-d_6)** δ (ppm): 9.07 (bs, 1H), 8.05-7.90 (m, 2H), 7.60-7.40 (m, 2H), 7.35-7.05 (m, 10H), 7.04 (td, *J* = 7.6 Hz, 1.5 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.60-5.70 (m, 3H), 4.95-4.50 (m, 5H), 3.70-2.80 (m, 8H). **HRMS** (calc.): 552.2750 [$M^{+\cdot}$ - NH_4], (found): 552.2746	1B
21	28		NH_2	4-{[4-benzyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	^{1}H NMR **($CDCl_3$)** δ (ppm): 7.83 (d, *J* = 8.2 Hz, 3H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, *J* = 6.2 Hz, 1H), 4.64 (d, *J* = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, *J* = 5.4 Hz), 1.63-1.53 (m, 12H).	1A

Ex.	Cpd	Y	X	Name	Characterization	Schm
22	29		NH_2	4-[(4-Amino-6-benzylamino-[1,3,5]triazin-2-ylamino)-methyl]-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d$_6$)** δ (ppm): 9.04 (s, 1H), 7.95 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 7.1 Hz, 2H), 7.38-7.15 (m, 6H), 7.00 (td, *J* = 8.0 Hz, 1.5 Hz, 1H), 6.86 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.67-6.25 (m, 3H), 5.85-5.55 (m, 3H), 4.61 (d, *J* = 6.3 Hz, 2H), 4.54 (d, *J* = 5.2 Hz, 2H). **HRMS** (calc.): 440.2073, (found): 440.2078	1A
23	30			4-{[6-(2-indanyl-amino)-4-(3-pyridinyl-methyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d$_6$)** δ (ppm): mixture of rotamers, 9.20-9.00 (m, 1H), 8.70-8.35 (m, 2H), 8.05-7.90 (m, 2H), 7.85-7.55 (m, 1H), 7.55-7.10 (m, 8H), 7.04 (dt, *J* = 7.6 Hz, 1.5 Hz, 1H), 6.91 (bd, *J* = 7.4 Hz, 1H), 6.71 (bt, *J* = 7.3 Hz, 1H), 6.80-6.00 (m, 3H), 4.84-4.50 (m, 7H), 3.34-3.12 (m, 2H), 3.00-2.80 (m, 2H). **HRMS** (calc.): 539.2546 [$M^{+\cdot}$ - NH_4], (found): 539.2533	1B
24	31			*N*-(2-Amino-phenyl)-4-[(4-piperidin-1-yl-6-pyrrolidin-1-yl-[1,3,5]triazin-2-ylamino)-methyl]-benzamide	**^{1}H NMR ($CDCl_3$)** δ (ppm): 7.89 (bs, 1H,), 7.82 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.09 (dt, *J* = 7.7 Hz, 1.6 Hz, 1H), 6.87-6.82 (m, 2H), 4.83 (bs, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.24 (m, 1H), 3.88 (bs, 1H), 2.04-1.96 (m, 2H), 1.70-1.52 (m, 10H), 1.46-1.38 (m, 2H).	1B

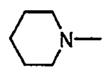
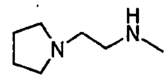
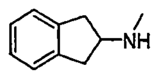
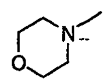
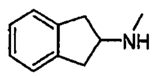
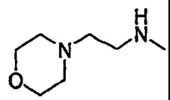
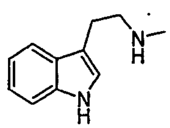
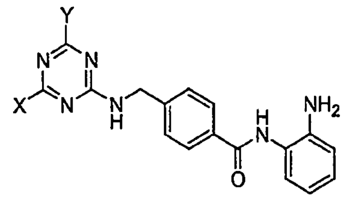
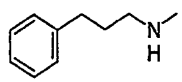
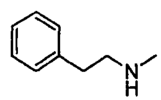
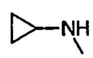
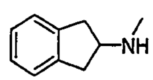
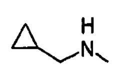
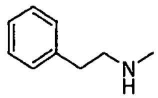
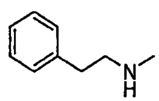
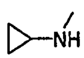
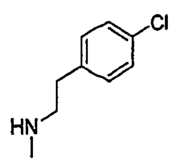
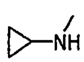
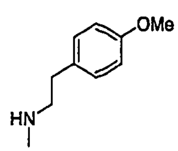
Ex.	Cpd	Y	X	Name	Characterization	Schm
25	32			*N*-(2-Amino-phenyl)-4-{[2-piperidin-1-yl-6-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-ylamino]-methyl}-benzamide	**^{1}H NMR ($CDCl_3$)** δ (ppm): 8.27 (bs, 1H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.29 (m, 3H), 7.05 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 6.81-6.76 (m, 2H), 5.62 (bs, 2H), 4.57 (bs, 2H), 3.91 (bs, 2H), 3.69 (m, 4H), 3.45 (m, 2H), 2.57 (t, *J* = 6.2 Hz, 2H), 2.47 (m, 4H), 1.71 (m, 4H), 1.59-1.50 (m, 6H).	1B
26	33			4-{[6-(2-indanyl-amino)-4-morpholin-4-yl-[1,3,5]-triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.07 (bs, 1H), 8.08-7.95 (m, 2H), 7.60-7.43 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.55-6.05 (m, 2H), 4.86-4.60 (m, 5H), 3.80-3.56 (m, 8H), 3.38-3.12 (m, 2H), 3.04-2.82 (m, 2H).	1B
27	34			*N*-(2-Amino-phenyl)-4-{[2-piperidin-1-yl-6-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-ylamino]-methyl}-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.08 (bs, 1H), 8.01 (bd, *J* = 7.4 Hz, 2H), 7.56-7.43 (m, 2H), 7.33 (bd, *J* = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.75 (m, 2H), 4.90-4.58 (m, 5H), 3.66-2.34 (m, 16H).	1B
28	35		NH_2	4-({4-Amino-6-[2-(1*H*-indol-3-yl)-ethylamino]-[1,3,5]triazin-2-ylamino}-methyl)-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 10.00 (s, 1H), 9.13 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.70-7.50 (m, 1H), 7.50-7.22 (m, 4H), 7.18-6.91 (m, 4H), 6.85 (d, *J* = 7.1 Hz, 1H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.40-5.90 (m, 3H), 4.75-4.50 (m, 2H), 4.37 (s, 2H), 3.62 (d, *J* = 6.3 Hz, 2H), 2.99 (s, 2H).	1A

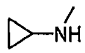
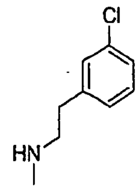
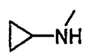
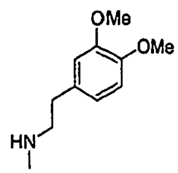
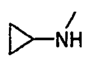
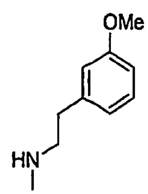
Table 2b

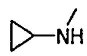
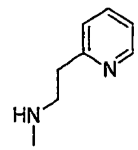
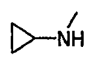
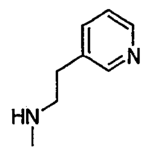
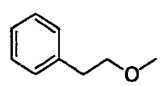
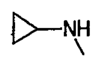
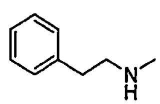


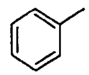
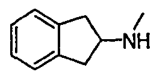
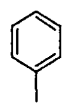
Ex.	Cpd	X	Y	Name	Characterization	Schm
329	470		NH_2	4-{[4-amino-6-(3-phenyl-propyl-1-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-*N*-(2-amino-phenyl)-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 9.03 (s, 1H), 7.96 (d, J=8.2 Hz, 2H), 7.46 (d, J=7.7 Hz, 2H), 7.35-7.10 (m, 6H), 7.00 (t, J=7.7 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.67 (t, J=7.7 Hz, 1H), 6.60-5.40 (m, 6H), 4.62 (s, 2H), 3.35 (dd, J=12.1, 6.9 Hz, 2H), 2.75-2.60 (m, 2H), 1.95-1.80 (m, 2H).	1A
330	471			*N*-(2-amino-phenyl)-4-[(4-cyclopropyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 9.04 (s, 1H), 7.96 (d, J=8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.98 (t, J=7.4 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (t, J=7.3 Hz, 1H), 6.20-5.50 (m, 3H), 4.80-4.50 (m, 4H), 3.65-3.45 (m, 2H), 3.00-2.60 (m, 2H), 0.80-0.40 (m, 4H).	1B
331	472			*N*-(2-amino-phenyl)-4-{[4-cyclopropyl-methylamino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 9.06 (bs, 1H), 8.00 (bd, J = 7.1, 2H), 7.50 (bs, 1H),), 7.33 (d, J = 6.6 Hz, 1H), 7.28-7.07 (m, 4H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.55-5.70 (m, 3H), 4.90-4.50 (m, 5H), 3.40-2.80 (m, 6H), 1.07 (bs, 1H), 0.44 (bs, 2H), 0.23 (bs, 2H).	1B

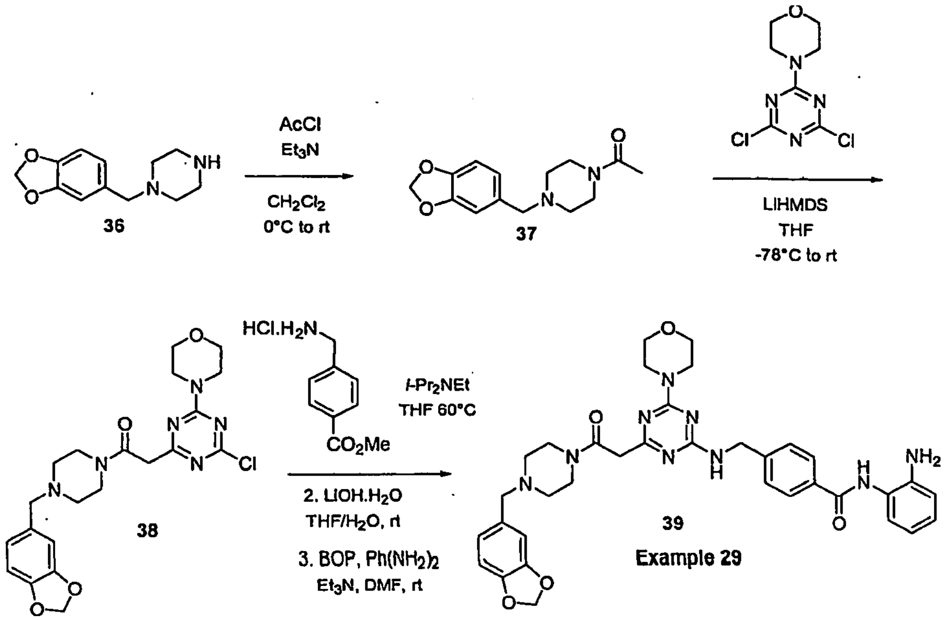
SUBSTITUTE SHEET (RULE 26)

Ex.	Cpd	X	Y	Name	Characterization	Schm
332	473		n-BuNH	N-(2-amino-phenyl)-4-[(4-n-butyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide	^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (s, 1H), 7.83 (d, J = 6.6 Hz, 2H), 7.45-7.05 (m, 8H), 7.08 (td, J = 7.8, 1.5 Hz, 1H), 6.84 (t, J = 8.1 Hz, 2H), 6.70-5.00 (m, 3H), 4.70-4.50 (m, 2H), 3.65-3.50 (m, 2H), 3.45-3.25 (m, 2H), 2.40-2.25 (m, 2H), 1.60-1.45 (m, 2H), 1.45-1.00 (m, 2H), 1.00-0.8 (m, 3).	1B
333	474		$MeOCH_2CH_2NH$	N-(2-amino-phenyl)-4-{[4-(2-methoxy-ethyl-1-amino)-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.02 (s), 8.58 (s), 8.40 (dd, J = 7.2, 2 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.51-7.40 (m, 2H), 7.70-6.90 (m, 7H), 6.86 (dd, J = 8.1, 1.2 Hz), 6.76 (dd, J = 7.5, 1.8 Hz), 6.67 (td, J = 7.8,1.5 Hz), 6.60-5.50 (m, 3H), 4.75-4.55 (m, 4H), 3.65-3.35 (m, 6H), 3.35-3.20 (s, 3H), 2.95-2.75 (m, 2H).	1B
334	475			N-(2-amino-phenyl)-4-{[4-(4-chloro-phenethyl-amino)-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.02 (s, 1H), 8.02-7.91 (m, 2H), 7.58-7.40 (m, 2H), 7.28 (s, 4H), 7.20-7.05 (m, 1H), 6.99 (td, J = 7.5, 1.8 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.67 (t, J = 6.9 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.65-3.40 (bs, 2H), 2.95-2.65 (m, 2H), 0.75-0.55 (m, 2H), 0.55-0.40 (m, 2H).	1B
335	476			N-(2-amino-phenyl)-4-{[6-cyclopropyl-amino-4-(4-methoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.55-7.72 (m, 4H), 7.55-6.75 (m, 9H), 6.75-5.30 (m, 3H), 4.69 (m, 2H), 3.85 (s, 3H), 3.63 (bs, 2H), 2.86 (m, 3H), 0.85 (bs, 2H), 0.61 (bs, 2H).	1B

Ex.	Cpd	X	Y	Name	Characterization	Schm
336	477			*N*-(2-amino-phenyl)-4-{[4-(3-chloro-phenethyl-amino)-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.03 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.60-7.37 (m, 2H), 7.37-7.12 (m, 5H), 6.99 (t, J = 6.9 Hz, 1H), 6.86 (d, J = 6.9 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.67-3.45 (m, 2H), 3.00-2.67 (m, 3H), 0.75-0.40 (m, 4H).	1B
337	478			*N*-(2-amino-phenyl)-4-{[6-cyclopropyl-amino-4-(3,4-dimethoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.29 (d, J = 8.1 Hz, 1H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), 6.95-6.72 (m, 4H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.20-5.60 (m, 3H), 4.78-4.52 (m, 4H), 3.75 (s, 6H), 3.65-3.42 (m, 2H), 2.95-2.65 (m, 3H), 0.72-0.40 (m, 4H).	1B
338	479			*N*-(2-amino-phenyl)-4-{[6-cyclopropyl-amino-4-(3-methoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.60-7.35 (m, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.99 (td, J = 7.5, 1.5 Hz, 1H), 6.90-6.70 (m, 4H), 6.67 (t, J = 7.8 Hz, 1H), 6.60-5.60 (m, 3H), 4.77-4.50 (m, 4H), 3.76 (s, 3H), 3.65-3.45 (m, 2H), 2.92-2.65 (m, 3H), 0.72-0.42 (m, 4H).	1B

Ex.	Cpd	X	Y	Name	Characterization	Schm
339	480			*N*-(2-amino-phenyl)-4-{[6-cyclopropyl-amino-4-(2-pyridin-2-yl-ethyl-1-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 9.03 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.60-7.40 (m, 2H), 7.35-7.08 (m, 3H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), 6.86 (dd, J = 8.1, 1.5 Hz, 1H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.80-3.60 (m, 2H), 3.15-2.90 (m, 2H), 2.90-2.65 (m, 1H), 0.73-0.40 (m, 4H).	1B
340	481			*N*-(2-amino-phenyl)-4-{[6-cyclopropyl-amino-4-(3-pyridin-2-yl-ethyl-1-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 9.20-9.00 (m, 1H), 8.70-8.50 (m, 2H), 8.00 and 7.88 (2d, J = 7.9 Hz, 2H), 7.75-7.43 (m, 3H), 7.38-6.67 (m, 5H), 6.22-5.78 (m, 3H), 4.80-4.55 (m, 4H), 3.61 (bs, 2H), 3.20-2.65 (m, 3H), 0.80-0.45 (m, 4H).	1B
341	482			*N*-(2-amino-phenyl)-4-[(4-cyclopropyl-amino-6-phenethyl-oxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 9.04 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.35-7.15 (m, 6H), 7.00 (td, J = 7.5, 1.5 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 7.18-6.35 (m, 2H), 4.75-4.30 (m, 6H), 3.10-2.92 (m, 2H), 0.75-0.63 (m, 2H), 0.57-0.48 (m, 2H).	1, 25
342	483		Me	*N*-(2-amino-phenyl)-4-[(6-methyl-4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide	**^{1}H NMR (300 MHz, acetone-d_6 + ε DMSO-d_6)** δ (ppm): mixture of rotamers, 9.62 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.80-7.44 (m, 3H), 7.40-7.10 (m, 8H), 7.01 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 4.85 (bs, 2H), 4.72-4.54 (m, 2H), 3.63-3.42 (m, 2H), 2.96-2.74 (m, 2H), 2.21 and 2.13 (2s, 3H).	30

Ex.	Cpd	X	Y	Name	Characterization	Schm
343	484		NH_2	*N*-(2-amino-phenyl)-4-{[4-amino-6-phenyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): mixture of rotamers, 9.08 (bs, 1H), 8.48-8.36 (m, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.63-7.42 (m, 5H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.19 (bs, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.35 and 6.25 (2bs, 2H), 4.87 and 4.75 (2d, *J* = 5.9 Hz, 2H), 4.65 (bs, 2H).	30
344	485			*N*-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-phenyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): mixture of rotamers, 9.14-8.96 (m, 1H), 8.54-8.30 (m, 2H), 8.09-7.95 (m, 2H), 7.68-7.40 (m, 5H), 7.38-7.08 (m, 6H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.94-6.76 (m, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 5.13-4.54 (m, 5H), 3.49-3.18 (m, 2H), 3.12-2.90 (m, 2H).	30



Example 29

***N*-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino}-methyl)-benzamide (compound 39)**

<u>Step 1: *N*-Acetyl-1-piperonylpiperazine (compound 37)</u>

[0175] To a stirred solution at 0°C of 1-piperonylpiperazine **36** (5.00 g, 22.7 mmol) in anhydrous CH_2Cl_2 (60 mL) was added Et_3N (6.33 mL, 45.4 mmol) followed by acetyl chloride (1.94 mL, 27.2 mmol). The reaction mixture was stirred 30 min. at 0°C and then 2 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 4/96) to afford the title compound **37** (5.52 g, 21.11 mmol, 93% yield) as a yellow solid. ^1H NMR: (300 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 1H), 6.72 (m, 2H), 5.92 (s, 2H), 3.59 (t, J = 5.1 Hz, 2H), 3.44-3.40 (m, 4H), 2.42 (dt, J = 5.1 Hz, 5.1 Hz, 4H), 2.06 (s, 3H).

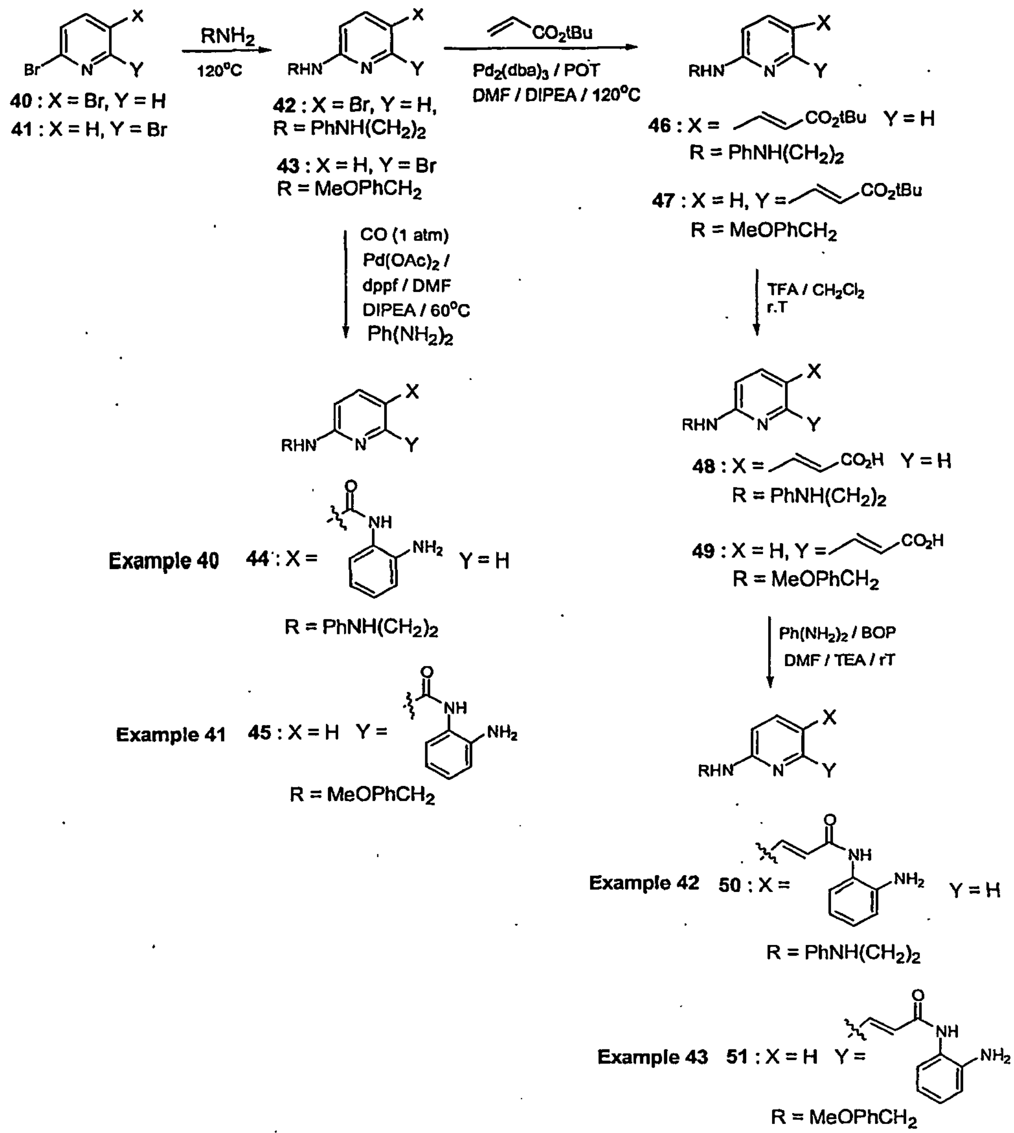
<u>Step 2: 2-Chloro-4-morpholin-4-yl-6-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-[1,3,5]triazine (compound 38)</u>

[0176] To a stirred solution of **37** (3.00 g, 11.4 mmol) in anhydrous THF (25 mL) at −78°C was slowly added a solution of LiHMDS (11.4 mL,

11.4 mmol, 1 M in THF). The reaction mixture was stirred 1 h at -78°C and a solution of 2,4-dichloro-6-morpholin-4-yl-[1,3,5]triazine (2.69 g, 11.4 mmol) in anhydrous THF (25 mL) was added. The reaction mixture was slowly warmed up at room temperature and the reaction was quenched after 16 h with a saturated aqueous solution of NH_4Cl. The THF was evaporated and the residue was diluted with AcOEt. The organic layer was successively washed with *sat.* NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 1/99→3/97) to afford the title compound **38** (4.84 g, 10.49 mmol, 92% yield) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.84 (s, 1H), 6.77-6.69 (m, 2H), 5.95 (s, 2H), 3.75-3.43 (m, 16H), 2.42 (m, 4H).

<u>Step 3: *N*-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino}-methyl)-benzamide (compound **39**)</u>

[0177] The title compound 39 was obtained following the same procedure as Example 1, step 5. ^1H NMR ($CDCl_3$) δ (ppm): 7.96 (bs, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.10 (dt, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.87-6.81 (m, 3H), 6.75-6.68 (m, 2H), 5.93 (s, 2H), 5.67 (bs, 1H), 4.64 (s, 2H), 3.90 (bs, 2H), 3.75-3.35 (m, 16H), 2.45-2.30 (m, 4H).



Example 40

N-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound 44)

Step 1: *N*-(5-Bromo-pyridin-2-yl)-*N'*-phenyl-ethane-1,2-diamine (compound 42)

[0178] A mixture of 2,5-dibromopyridine **40** (2.08 g, 8.6 mmol) and phenyl-1,2-ethyldiamine (1.98 g; 14.6 mmol, 1.7 equiv.) was stirred under nitrogen at 120°C for 6h. After cooling down to room temperature, the solid mixture was ground in a mortar, dissolved in ethyl acetate (200 mL), washed with saturated $NaHCO_3$ (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated. After a quick purification through a short chromatographic column (silica gel, elution 50% ether

in hexanes), a pale yellow solid **42** (1.75 g, 6.01 mmol, 70% yield) was obtained. ^{13}C NMR (300 MHz, acetone-d_6) δ (ppm): 158.6, 149.6, 148.8, 139.9, 129.8, 117.1, 113.1, 110.8, 106.6, 43.9, 41.5. LMRS = 294.0 (M+1).

Step 2: *N*-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound **44**)

[0179] A mixture of 5-bromo-2-*N*-alkanyl-2-aminopyridine **42** (352 mg, 1.2 mmol), 1,2-phenylenediamine (3.95 mmol, 3.3 equiv.), $Pd(OAc)_2$ (0.31 mmol, 26% mol) and 1,1'-bis (diphenylphosphino) ferrocene (124 mg, 0.22 mmol) was suspended in degassed DMF (3mL), treated with diisopropylethyl amine (0.9 mL, 5.2 mmol) and the system flushed with CO. The reaction mixture was warmed up to 60°C and stirred under CO (balloon) for 18 h at this temperature. After evaporation of the DMF under *vacuo*, the residue was purified through a chromatographic column (silica gel, elution 3% to 6% methanol in dichloromethane) to give 258 mg (0.74 mmol, 62 % yield) of the aminoanilide **44**. ^{1}H-NMR (CD_3OD-*d4*), δ (ppm): 8.67 (d, *J* = 2.2 Hz, 1H), 7.97 (dd, *J*= 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt, *J*= 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, *J* = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.35 (t, *J* = 6.3 Hz, 2H).

Example 41

***N*-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide (compound 45)**

Step 1: *N*-(5-Bromo-pyridin-2-yl)-4-methoxybenzylamine (compound **43**)

[0180] A mixture of 2,6-dibromopyridine **41** (6.03 mmol, 2 equiv.) and *para*-methoxybenzyl amine (413 mg, 3.01 mmol) was stirred under nitrogen at 120°C for 6h. After identical work-up procedure described before and purification through a pad of silica gel (elution 50% ether in hexanes), a pale yellow solid **43** (773 mg, 2.60 mmol, 87% yield) was obtained. ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 159.1, 139.7, 132.1, 130.5, 128.9, 127.2, 116.2, 114.3, 104.8, 55.4, 46.0. LMRS = 295.0 (M+1).

Step 2: *N*-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide (compound **45**)

[0181] Following the procedure described in Example 40, step 2, but substituting **43** for **42**, the title compound **45** was obtained in 61% yield.

Example 42

***N*-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound 50)**

Step 2: 3-[6-(2-Phenylamino-ethylamino)- pyridin-3-yl)-acrylic acid *tert*-butyl ester (compound **46**)

[0182] In a 50 mL flask, a mixture of **42** (308 mg, 1.05 mmol), tert-butylacrylate (0.8 mL, 5.5 mmol), diisopropylethylamine (0.8 mL, 4.6 mmol), tri-*o*-tolylphosphine (POT, 192 mg, 0.63 mmol), $Pd_2(dba)_3$ (73 mg, 0.08 mmol) in anhydrous DMF (4 mL) was stirred at 120°C (preheated oil bath) for 2h under nitrogen. After DMF removal, the crude residue was submitted to a chromatographic purification (column silica gel, 50% ether in hexanes) to afford 316 mg of **46** (88% yield). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 166.6, 159.3, 149.6, 147.8, 140.7, 134.9, 129.1, 119.8, 117.3, 115.9, 112.6, 107.8, 80.0, 43.5, 40.9, 28.1. LRMS = 340.3 (M+1).

Step 3: 3-[6-(2-Phenylamino-ethylamino)- pyridin-3-yl)-acrylic acid (compound **48**)

[0183] Ester **46** (0.93 mmol) was dissolved 40 % TFA in dichloromethane (10 mL) and the solution stirred at room temperature overnight. The solvent was removed under *vacuo* distilling with acetonitrile (3x10 mL) and stored under high vacuum for 6h. The solid residue **48** was employed for the next reaction without further purification. LRMS = 284.1 (M+1).

Step 4: *N*-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound **50**)

[0184] A mixture of acid **48** (0.93 mmol), BOP (495 mg, 1.12 mmol) and 1,2-phenylenediamine (124 mg, 1.15 mmol) were dissolved in dry acetonitrile (4 mL) and treated with triethylamine (0.8 mL, 5.7 mmol). The solution was stirred under nitrogen at room temperature for 16h. After concentration under *vacuo*, the crude was purified through chromatographic column (5% methanol in dichloromethane), then was

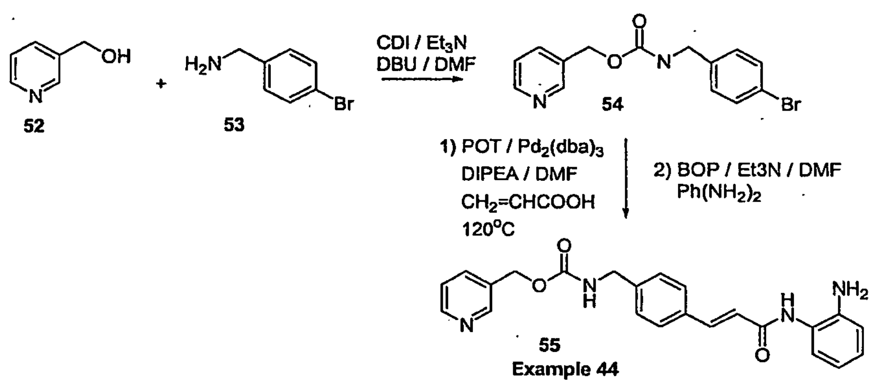
crystallized from chloroform to give **50** (247 mg, 71% yield). ^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J= 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H).

Example 43

***N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound 51)**

Step 2: *N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound **51**)

[0185] Following the procedure described in Example 42, steps 2, 3, 4, but substituting **43** for **42**, the title compound **51** was obtained in 50% yield (on 2 steps). ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H).



Example 44

4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

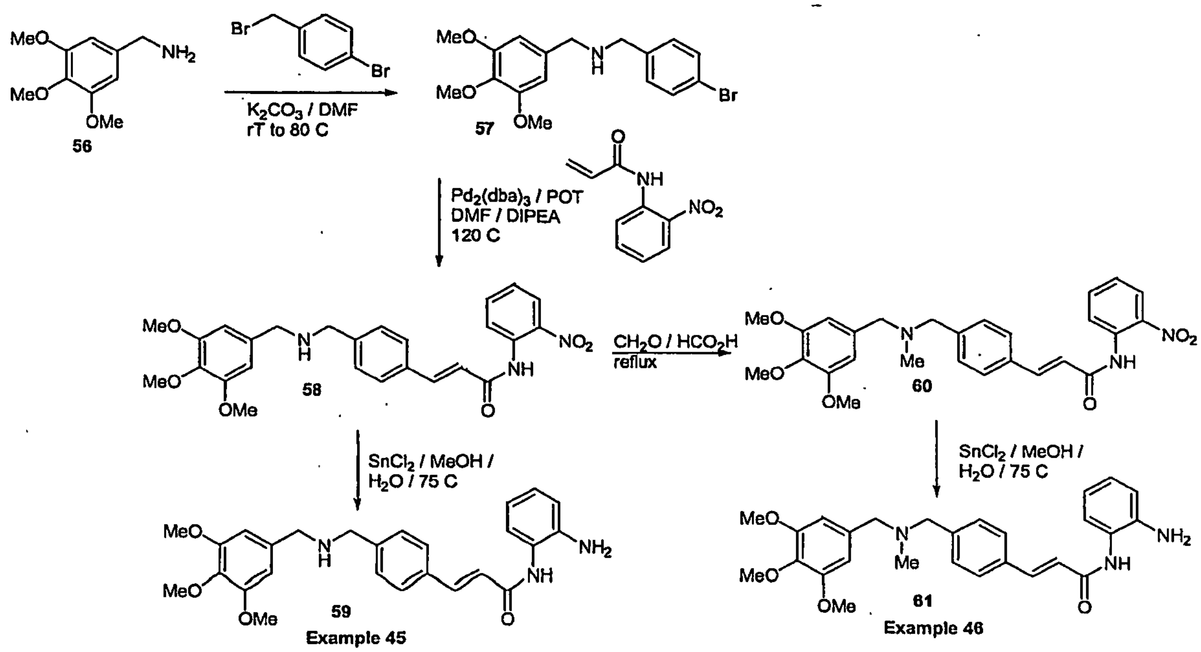
Step 1: (4-bromo-benzyl)-carbamic acid pyridin-3-yl-methyl ester (compound 54)

[0186] 4-bromobenzylamine HCl (3.0g, 13.4 mmol) was dissolved in DMF (60 mL) at rt and then Et_3N (4.13 mL, 29.7 mmol) was added dropwise over 10 min to give cloudy solution. To this, DBU (2.42 mL, 16.2 mmol)

and 1,1'-carbonyl diimidazole (2.41g, 14.8 mmol) were added. After being stirred for 1 h at rt, 3-pyridylcarbinol (1.44 mL, 14.8 mmol) was added dropwise over 10 min. The resulting reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue obtained was diluted with ether/EtOAc (9:1) and then washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and then concentrated to give the crude product which was recrystallized from EtOAc to give 2.55g of product **54** (59% yield, LRMS = 323 (M+1).

Step 2: 4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

[0187] Following the procedure described in Example 42, steps 2, 3, but substituting **54** for **42**, and acrylic acid for tert-butyl acrylate the title compound **55** was obtained in an overall yield of 20%. ^{1}H NMR: (DMSO-d6) δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d, J = 3.3 Hz, 1H), 7.85 (d, J = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, J = 7.69 Hz, 1H), 6.89 (dd, J = 7.14 Hz, J = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, J = 7.1 Hz, J = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H).



Example 45

N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound 59)

Step 1: (4-Bromo-benzyl)-(3,4,5-trimethoxy-benzyl)-amine (compound 57)

[0188] To a stirred suspension of K_2CO_3 (522 mg, 3.77 mmol) in dry DMF was added 3,4,5-trimethoxybenzylamine (1.10 mL, 6.44 mmol, 2.2 equiv.) followed by a solution of p-bromo benzylbromide (0.73 g, 2.91 mmol) in dry DMF (8 mL). The mixture was stirred at room temperature under nitrogen for two days in the dark, diluted with dichloromethane (200 mL), washed with brine, dried (MgSO4), filtered and concentrated. The crude residue was purified by chromatographic column on silica gel (elution 5% methanol in dichloromethane) to give 2.59 mmol (89% yield) of dibenzylamine **57**. ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 152.5, 138.8, 136.1, 135.4, 130.6, 129.2, 119.8, 104.2, 59.9, 55.3, 52.6, 51.7. LRMS = 368.4 (M+1).

Step 2: N-(2-Nitro-phenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound **58**)

Preparation of the nitroacrylanilide

[0189] To a mixture of 2-nitroaniline (1.73 g, 12.5 mmol), DMAP (321 mg, 2.6 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (308 mg) in dry dichloromethane (50 mL) at 0°C was added triethylamine (10.6 mL, 76

mmol) followed by acryloylchloride (3.2 mL, 38 mmol, 3.0 equiv.), and the mixture was stirred at room temperature for 16h. The solution was diluted with dichloromethane (250 mL), cooled to 0°C and the excess of reagent quenched with saturated $NaHCO_3$ (stirring for 1 h). The organic layer was then washed (5% $KHSO_4$, then brine), dried ($MgSO_4$), filtered and concentrated under reduced pressure. After purification through chromatographic column on silica gel (elution 50% ether in hexanes), 642 mg (3.34 mmol, 27% yield) of the amide was obtained. ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 163.6, 136.0, 135.6, 134.5, 131.3, 128.6, 125.4, 123.1, 121.8. LRMS = 193.2 (M+1).

Step 3: *N*-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (**59**)

[0190] A mixture of nitro-compound **58** (127 mg, 0.27 mmol), $SnCl_2$ (429 mg, 2.26 mmol, 8.4 equiv.) and NH_4OAc (445 mg) was suspended in methanol (9.5 mL) and water (1.5 mL), and the mixture was heated at 70°C for 45 min. The mixture was diluted with ethylacetate (100 mL) and washed with brine and then saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatographic column on silica gel (elution 5 to 10% methanol in dichloromethane) gave 52 mg (43% yield) of **59**. ^1H-NMR ($CDCl_3$), δ (ppm): 8.25 (bs, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, J = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H).

Example 46

***N*-(2-aminophenyl)-3-(4-{[(3,4,5-trimethoxy-benzyl)-amino]-methyl}-phenyl)-acrylamide (compound 61)**

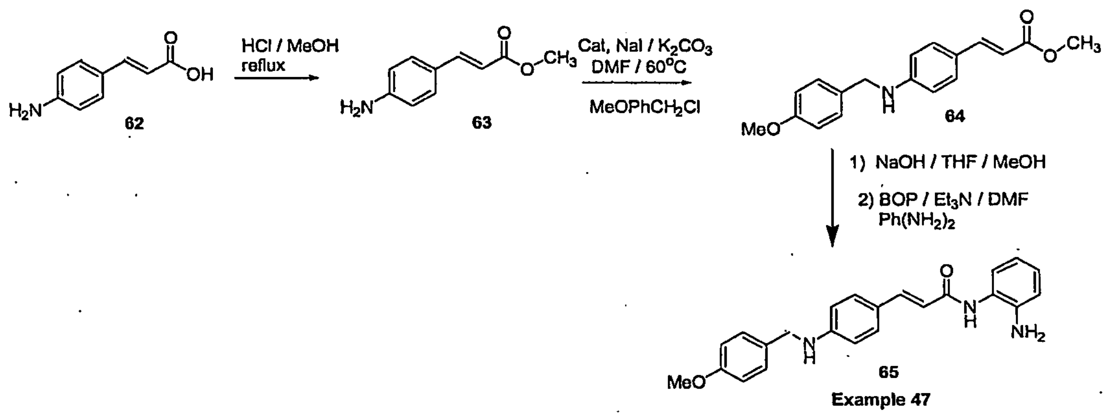
Step 1: 3-{4-{[Methyl-(3,4,5-trimethoxy-benzyl)-amino]-methyl}-phenyl)-*N*-(2-nitro-phenyl)-acrylamide (compound **60**)

[0191] Amine **58** (180.2 mg, 0.38 mmol) was dissolved in 88% of HCO_2H (6 mL), treated with excess of paraformaldehyde (7.67 mmol) and the mixture stirred at 70°C for 2.5h. A saturated $NaHCO_3$ solution, was added slowly, extracted with dichloromethane (2 x 75 mL), dried ($MgSO_4$), filtered and concentrated. After chromatographic column on silica gel (elution 3 to 5% methanol in dichloromethane), pure *N*-methyl amine **60** (118 mg, 63% yield) was obtained. ^{13}C NMR (300 MHz,

$CDCl_3$) δ (ppm): 164.5, 153.1, 143.5, 142.3, 136.8, 136.1, 136.0, 135.3, 134.9, 132.9, 129.3, 128.2, 125.8, 123.1, 122.2, 120.3, 105.4, 62.2, 61.2, 60.8, 56.0, 42.5. LRMS = 492.5 (M+1).

Step 2: *N*-(2-aminophenyl)-3-(4-{[(3,4,5-trimethoxy-benzyl)-amino]-methyl}- phenyl)-acrylamide (compound **61**)

[0192] Following the procedure described in Example 45, step 3, but substituting the nitro-compound **60** for **58**, the title compound **61** was obtained in 72% yield. ^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, J = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H).



Example 47

***N*-(2-aminophenyl)-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylamide (compound 65)**

Step 1: Methyl-3-(4-amino-phenyl)-acrylate hydrochloride (compound **63**)

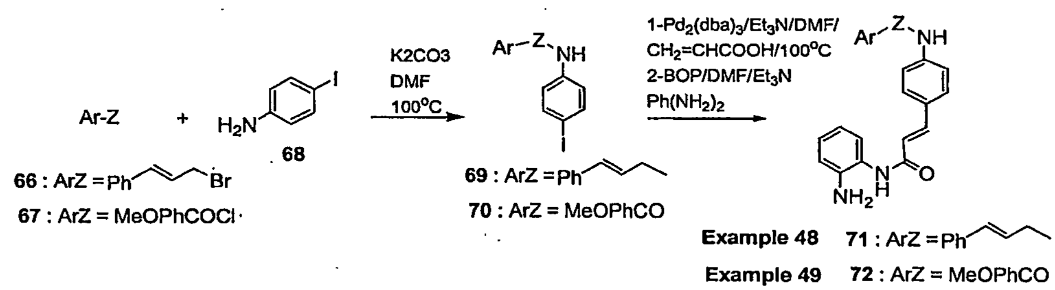
[0193] 4-amino-cinnamic acid (10.41 g, 0.052 mol) was dissolved in methanol (100 mL) at rt. A solution of HCl in dioxane (15.6 mL, 4 N) was then added. The reaction mixture was heated at reflux overnight. The clear solution was evaporated to a half volume and then settled down at rt. The white suspension obtained was collected by vacuum filtration. The mother liquid was evaporated again to a quart volume and cooled down to rt. The suspension was filtered again. The combined the solid collected from two filtration was dried *in vacuo* to give 7.16 g of **63** (64.3% yield). LRMS: 178 (M+1).

Step 2: Methyl-3-{4-(4-methoxy-benzylamino)-phenyl}- acrylate hydrochloride (compound **64**)

[0194] To a suspension of compound **63** (3.57 g, 16.7 mmol) in DMF (30 mL) was added Et_3N. after 10 min 4-methoxybenzyl chloride (2.0 g, 12.8 mmol), NaI (0.38 g, 2.6 mmol) and K_2CO_3 (3.53 g, 25.5 mmol) were added successively. The mixture was heated at 60°C overnight and evaporated to dryness. The residue was partitioned between $NaHCO_3$ sat. solution (50 mL) and EtOAc (50mLx3). The combined organic layers were washed with brine and then evaporated to dryness. The residue was purified by flash chromatography and then recrystallized from isopropylalcohol to give 1.16 g **64** (yield 30.6%, LRMS = 298) and 1.46g of **63** (49% recovered yield).

Step 3: *N*-(2-aminophenyl)-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylamide (compound 65)

[0195] Following the procedure described in Example 42, step 4, but substituting **64** for **48**, the title compound **65** was obtained in 32% yield. ^1H NMR: (DMSO-d6) δ (ppm): 9.15 (s, 1H), 7.24 -7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).



Example 48

N-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (compound 71)

Step 1: *N*-(4-Iodo-phenyl)-(3-phenyl-allyl)-amine (compound 69)

[0196] Following the procedure described in Example 47, step 2, but substituting **68** for **63**, the title compound **69** was obtained in 70% yield. LRMS = 288 (M+1)

Step 2: *N*-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (71)

[0197] Following the procedure described in Example 42, steps 2, 4, but substituting **69** for **42**, and acrylic acid for tert-butyl acrylate the title compound **71** was obtained in an overall yield of 60%. ^1H NMR:

(DMSO-d_6) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).

Example 49

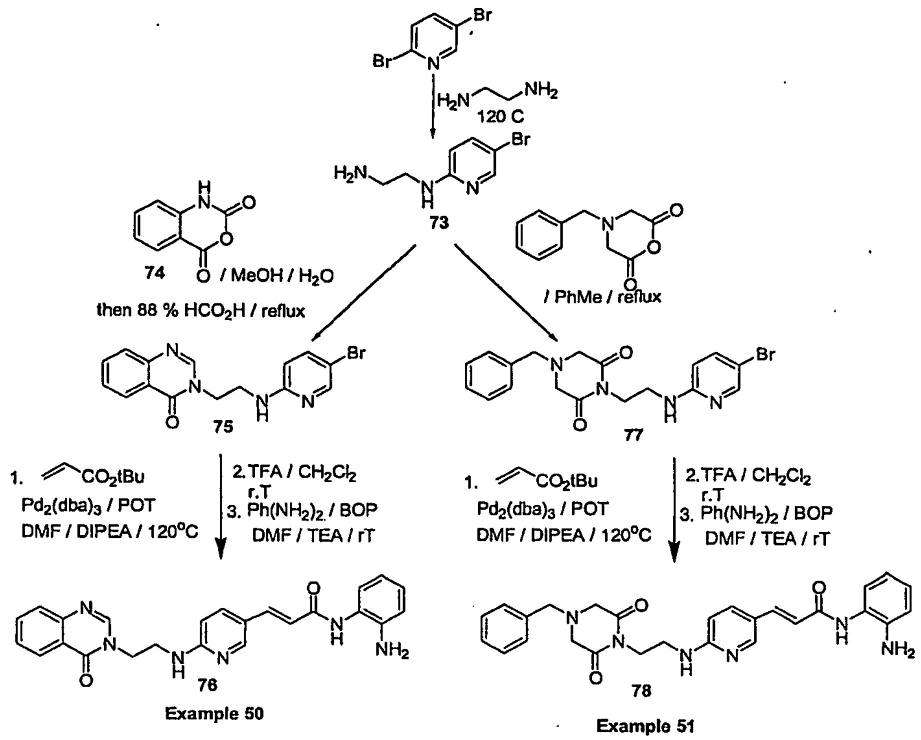
N-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)

Step 1: *N*-(4-Iodo-phenyl)-4-methoxy-benzamide (compound **70**)

[0198] Following the procedure described in Example 47, step 2, but substituting **68** for **63**, the title compound **70** was obtained in 90% yield. LRMS = 354.0 (M+1)

Step 2: *N*-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound **72**)

[0199] Following the procedure described in Example 42, steps 2, 4, but substituting **70** for **42**, and acrylic acid for tert-butyl acrylate the title compound **72** was obtained in an overall yield of 90%. ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.4 (bs, 1H), 7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).



Example 50

N-(2-aminophenyl)-3-{6-[2-(4-oxo-4H-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 76)

Step 1: N-(5-Bromo-pyridin-2-yl)-ethane-1,2-diamine (compound 73)

[0200] Following the procedure described in Example 40, step 1, but using 1,2-diaminoethane as alkyl amine, the title compound **73** was obtained in 84% yield. ^{13}C NMR (300 MHz, CD_3OD): 159.1, 148.7, 140.7, 111.7, 107.2, 44.3, 41.7. LRMS = 218.1 (M+1)

Step 2: 3-[2-(5-Bromo-pyridin-2-ylamino)-ethyl]-3H-quinazolin-4-one (compound 75)

[0201] A suspension of primary amine **73** (1.17 g, 5.40 mmol) and isatoic anhydride **74** (880 mg, 5.40 mmol) in methanol (25 mL) was stirred for 3 h at 50°C and then concentrated. The resulting oily residue was dissolved in 88% formic acid (20 mL) and refluxed overnight. After removal of formic acid, the solid residue was purified through column chromatography on silica gel (5% methanol in dichloromethane) to give 1.24 g (3.6 mmol, 67% yield) of **75**. ^{13}C NMR (300 MHz, $CDCl_3$): 161.6, 156.8, 147.7, 147.6, 147.2, 139.8, 134.5, 127.4, 126.8, 126.3, 121.6, 110.1, 107.0, 46.3, 40.1. LRMS = 347.1 (M+1).

Step 3: *N*-(2-aminophenyl)-3-{6-[2-(4-oxo-4*H*-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 76)

[0202] Following the procedure described in Example 42, steps 2 to 4, but substituting **75** for **42**, the title compound **76** was obtained in an overall yield of 68 %. ^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H).

Example 51

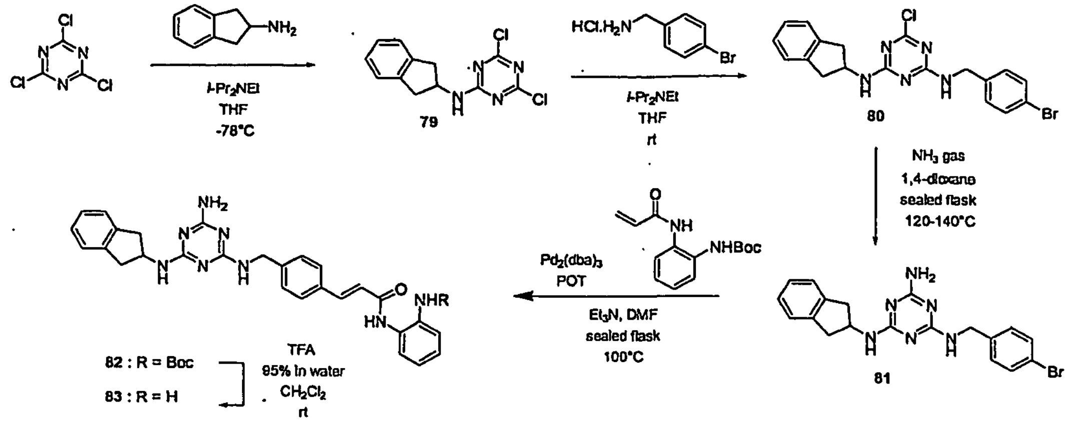
N-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 78)

Step 2: 4-Benzyl-1-[2-(5-bromo-pyridin-2-ylamino)-ethyl]-piperazine-2,6-dione (compound 77)

[0203] A suspension of benzyliminodiacetic acid (702 mg, 3.15 mmol) and acetic anhydride (15 mL) was stirred at 120°C for 45 min. The reaction mixture was diluted with dry toluene and concentrated in *vacuo* to remove the volatiles. The residue was dissolved in dry toluene (15 mL) and transferred via cannula to a reaction flask containing the amine **73** (475 mg, 3.2 mmol). The mixture was heated at 90°C for 16 h, concentrated and chromatographed by column on silica gel (elution 5% methanol in dichloromethane) to give 684mg (1.70 mmol, 54% yield) of **77**.

Step 3: *N*-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 78)

[0204] Following the procedure described in Example 42, steps 2 to 4, but substituting **77** for **42**, the title compound **78** was obtained in an overall yield of 60%. ^{1}H-NMR (CD_3OD-*d4*), δ (ppm): 8.09 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.38 (s, 4H).



Example 52

Example 52

(*E*)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-*N*-(2-amino-phenyl)-cinnamide (compound 83)

Step 1: 4,6-Dichloro-2-(2-indanyl-amino)-[1,3,5]triazine (compound **79**)

[0205] To a stirred solution at −78°C of cyanuric chloride (13.15 g, 71.33 mmol) in anhydrous THF (100 mL) under nitrogen was slowly canulated a solution of 2-aminoindan (10.00 g, 75.08 mmol), *i*-Pr_2NEt (14.39 mL, 82.59 mmol) in anhydrous THF (60 mL). After 50 min, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 2/98→5/95) and by co-precipitation (AcOEt/hexanes) to afford the title compound **79** (18.51 g, 65.78 mmol, 92% yield) as a beige powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29-7.18 (m, 4H), 6.02 (bd, J = 6.3 Hz, 1H), 4.94-4.84 (m, 1H), 3.41 (dd, J = 16.2, 6.9 Hz, 2H), 2.89 (dd, J = 16.1, 4.5 Hz, 2H).

Step 2: 2-(4-Bromo-benzyl-amino)-4-chloro-6-(2-indanyl-amino)-[1,3,5]triazine (compound **80**)

[0206] To a stirred solution at room temperature of **79** (2.68 g, 9.52 mmol) in anhydrous THF (50 mL) under nitrogen were added *i*-Pr_2NEt (4.79 mL, 27.53 mmol) and 4-bromobenzylamine.HCl (2.45 g, 11.01 mmol), respectively. After 17 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After

separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($AcOEt/CH_2Cl_2$: 3/97→5/95) to afford the title compound **80** (4.00 g, 9.29 mmol, 97% yield) as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): mixture of rotamers, 7.52-7.42 (m, 2H), 7.26-7.11 (m, 6H), 6.51 and 6.12 (2 m, 1H), 5.72-5.46 (m, 1H), 4.94-4.64 (m, 1H), 4.62-4.46 (m, 2H), 3.43-3.16 (m, 2H), 2.92-2.74 (m, 2H).

Step 3: 4-Amino-2-(4-bromo-benzyl-amino)-6-(2-indanyl-amino)-[1,3,5]triazine (compound **81**)

[0207] In a 75 mL sealed flask, a solution of **80** (2.05 g, 4.76 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH_3 gas for 5 min, and warmed to 140°C for 18 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH_3 gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 24 h. Then, the reaction mixture was allowed to cool to room temperature, poured into 1N HCl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 5/95) to afford the title compound **81** (1.96 g, 4.76 mmol, quantitative yield) as a colorless foam. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 8.2 Hz, 2H), 7.25-7.12 (m, 6H), 5.70-5.10 (m, 2H), 5.00-4.65 (m, 3H), 4.52 (bs, 2H), 3.40-3.10 (m, 2H), 2.90-2.65 (m, 2H).

Step 4: (*E*)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-*N*-[2-(*N*-*t*-butoxycarbonyl)-amino-phenyl]-cinamide (compound **82**)

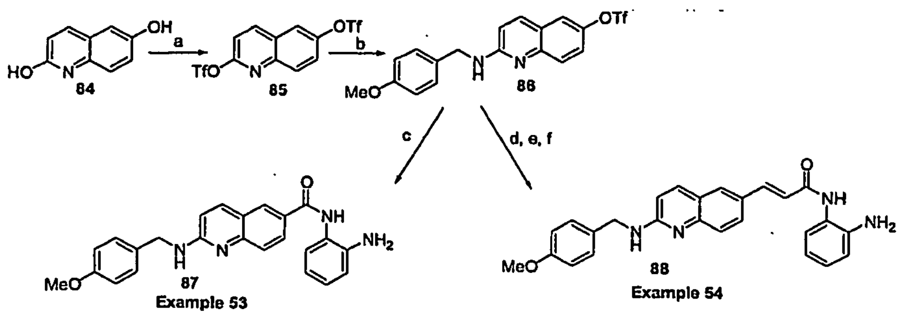
Preparation of *N*-[2-(*N*-*t*-Butoxycarbonyl)-amino-phenyl]-acrylamide

[0208] Following the procedure described in Example 45, step 2, but substituting the nitro-compound 2-(*N*-*t*-butoxycarbonyl)-amino-aniline for 2-nitroaniline, the title compound was obtained in 77% yield. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (bs, 1H), 7.60-7.45 (m, 1H), 7.38-7.28 (m, 1H), 7.20-7.05 (m, 2H), 6.98 (bs, 1H), 6.41 (dd, J = 17.0 Hz, 1.1 Hz, 1H), 6.25 (dd, J = 16.9 Hz, 10.0 Hz, 1H), 5.76 (dd, J = 10.2 Hz, 1.4 Hz, 1H), 1.52 (s, 9H).

[0209] In a 50 mL sealed flask, a solution of **81** (300 mg, 0.73 mmol), the acrylamide (230 mg, 0.88 mmol), Et_3N (407 µl, 2.92 mmol), tri-*o*-tolylphosphine (POT, 13 mg, 0.04 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol) in anhydrous DMF (10 mL) was stirred at room temperature, saturated with N_2 gas for 15 min, and warmed to 100°C for 15 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 2/98→5/95) to afford the title compound **82** (240 mg, 0.41 mmol, 56% yield) as a beige solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.46 (bs, 1H), 7.71 (bd, *J* = 15.7 Hz, 1H), 7.62-7.05 (m, 13H), 6.54 (bd, *J* = 15.9 Hz, 1H), 5.95-4.90 (m, 4H), 4.85-4.48 (m, 3H), 3.40-3.14 (m, 2H), 2.90-2.70 (m, 2H), 1.52 (s, 9H).

Step 5: (*E*)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-*N*-(2-amino-phenyl)-cinnamide (compound **83**)

[0210] To a stirred solution at room temperature of **82** (230 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added TFA (1 mL, 95% in water). After 18 h, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 5/95) to afford the title compound **83** (170 mg, 0.35 mmol, 89% yield) as a yellow solid. ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 8.87 (bs, 1H), 7.69 (d, *J* = 15.7 Hz, 1H), 7.59 (bd, *J* = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.69 (td, *J* = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H).



a. Tf_2O / Py / DMAP / 0 C
b. p-methoxybenzylamine / 120 C
c. 1,2-phenylenediamine / CO (40 psi) / $Pd(OAc)_2$ / dppf / DMF / DIPEA / 70 C
d. t Butylacrylate / $Pd_2(dba)_3$ / POT / DMF / DIPEA / 120 C
e. TFA / DCM / rT
f. 1,2-phenylenediamine / BOP/ DMF / TEA / rT

Example 53

N-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound 87)

Step 1: 2,6-ditrifluoromethanesulfonyloxy-quinoline (compound **85**):

[0211] A solution of 2,6-dihydroxyquinoline **84** (1.254 g, 7.78 mmol) and DMAP (a few crystals) in dry pyridine (15 mL) was treated with neat trifluoromethanesulfonic anhydride (5.2 g, 18,4 mmol, 1.2 equiv.) and stirred at 0°C for 5 h. This solution was then poured on a mixture brine/sat $NaHCO_3$ and extracted with dichloromethane (2 x 150 mL), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel (30% to 50% ether in hexanes) gave 2.58 g (6.1 mmol, 78% yield) of **85**. ^{13}C NMR (300 MHz, $CDCl_3$): 154.5, 147.8, 144.6, 142.0, 131.6, 127.8, 124.9, 119.3, 118.7, 114.9. LRMS = 426.0 (M+1).

Step 2: *N*-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound **87**)

[0212] Following the procedure described in Example 40, steps 1, 2, but substituting **85** for **40**, the title compound **87** was obtained in 92% yield. ^1H-NMR (DMSO-*d6*), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H).

Example 54

N-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)

Step 3: *N*-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)

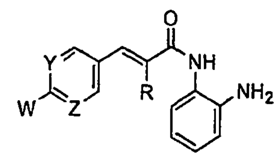
[0213] Following the procedure described in Example 42, steps 1 to 4, but substituting **85** for **40**, the title compound **88** was obtained in an overall yield of 71%. ^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H).

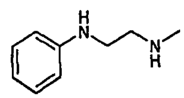
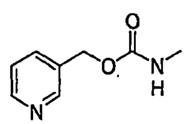
Examples 55-84

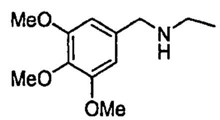
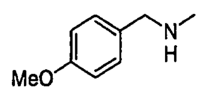
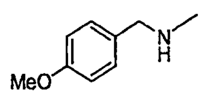
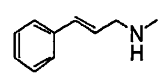
[0214] Examples 55 to 84 describe the preparation of compounds **89** to **118** using the same procedures as described for compounds **44** to **88** in Examples 40 to 54. Characterization data are presented in Tables 3a-d.

Table 3a

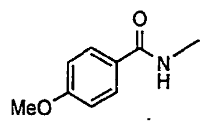
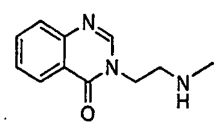
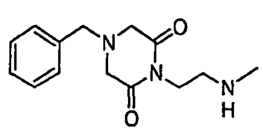
Characterization of Compounds Prepared in Examples 42-84

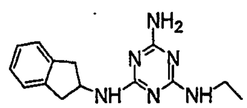
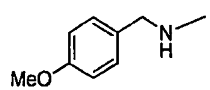
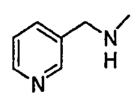


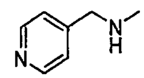
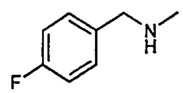
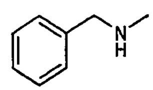
Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
42	50		N	CH	H	*N*-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.25 (bs, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 15.7 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 1.0 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 2H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.75 (dt, J= 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, *J* = 6.3 Hz, 2H)	3
44	55b		CH	CH	H	{4-[2-(2-amino-phenylcarbamoyl)-vinyl]-phenyl}-carbamic acid pyridin-3-yl methyl ester	**^{1}H NMR: (DMSO-d6)** δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d, *J* = 3.3 Hz, 1H), 7.85 (d, *J* = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, *J* = 7.69 Hz, 1H), 6.89 (dd, *J* = 7.14 Hz, *J* = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, *J* = 7.1 Hz, *J* = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H).	4

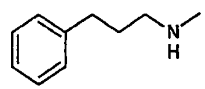
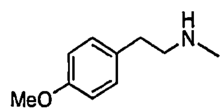
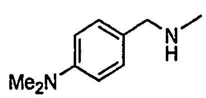
Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
45	59		CH	CH	H	*N*-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide	**^{1}H-NMR ($CDCl_3$)**, δ (ppm): 8.25 (bs, 1H), 7.59 (d, *J* = 15.6 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, *J* = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H).	5
46	61b		N	CH	Me	*N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-3-yl]-2-methyl-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, *J* = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H).	3
47	65		CH	CH	H	*N*-(2-amino-phenyl)-3-[4-(4-methoxy-benzylamino)-phenyl]-acrylamide	**^{1}H NMR: (DMSO-d6)** δ (ppm): 9.15 (s, 1H), 7.24 -7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, *J* = 5.77 Hz, 2H).	6
48	71		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide	**^{1}H NMR: (DMSO-d_6)** δ (ppm): 9.22 (bs, 1H), 7.45 (d, *J* = 6.9 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.26 (dt, *J* = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, *J* = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).	7

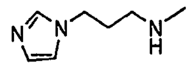
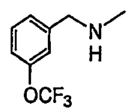
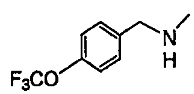
SUBSTITUTE SHEET (RULE 26)

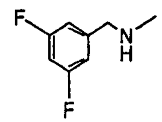
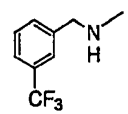
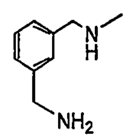
Ex	Cpd	W	Y	Z	R	Name	Characterization	Schm
49	72		CH	CH	H	*N*-{4-[2-(2-Amino-phenylcarbamoyl)-vinyl]-phenyl}-4-methoxy-benzamide	**^{1}H NMR: (DMSO-d_6)** δ (ppm): 9.4 (bs, 1H), 7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).	7
50	76		N	CH	H	*N*-(2-aminophenyl)-3-{6-[2-(4-oxo-4*H*-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H).	8
51	78		N	CH	H	*N*-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide	**^{1}H-NMR (CD_3OD-*d4*)**, δ (ppm): 8.09 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.38 (s, 4H).	8

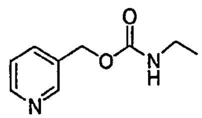
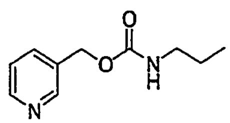
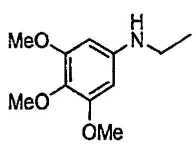
Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
52	83		CH	CH	H	(*E*)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-cinamide	**^{1}H NMR (300 MHz, acetone-d_6)** δ (ppm): 8.87 (bs, 1H), 7.69 (d, J = 15.7 Hz, 1H), 7.59 (bd, J = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H).	9
55	89		N	CH	H	*N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-3-yl]-acrylamide	^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.24 (bs, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 5.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.90 (m, 1H), 6.88 (dd, J = 8.5 Hz, 2H), 6.74 (d, J = 6.9 Hz, 1H), 6.58 (m, 3H), 4.92 (bs, 2H), 4.45 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H).	3
56	90		N	CH	H	*N*-(2-aminophenyl)-3-{6-[(pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-acrylamide	**^{1}H-NMR (CD_3OD-*d4*)**, δ (ppm): 8.47 (bs, 1H), 8.33 (bs, 1H), 8.02 (m, 1H), 7.73 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.29 (m, 1H), 7.14 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.66 (t, J = 7.9 Hz, 1H), 6.53 (m, 2H), 4.54 (m, 2H), 3.59 (bs, 2H).	3

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
57	91		N	CH	H	*N*-(2-aminophenyl)-3-{6-[(pyridin-4-ylmethyl)-amino]-pyridin-3-yl}-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.27 (bs, 1H), 8.48 (dd, J = 1.6 Hz, 4.4, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.70 (m 2H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (m 3H), 6.90 (t, J = 6.9 Hz, 1H), 6.73 (d, J = 6.9 Hz, 1H), 6.58 (m 4H), 4.98 (bs, 2H), 4.57 (d, J = 6.0 Hz, 2H).	3
58	92		N	CH	H	*N*-(2-aminophenyl)-3-[6-(4-fluoro-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.24 (bs, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 0.8 Hz, 1H), 7.60 (t, J = 5.8 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.36 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.73 (dd, J = 6.9 Hz, 1.0 Hz, 1H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.50 (d, J = 6.0 Hz, 2H).	3
59	93		N	CH	H	*N*-(2-aminophenyl)-3-(6-benzylamino-pyridin-3-yl)-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.24 (bs, 1H), 8.17 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.60 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.31 (m, 5H), 7.23 (m, 1H), 6.89 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.58 (m 3H), 4.92 (bs, 2H), 4.53 (d, J = 6.0 Hz, 2H)	3

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
60	94		N	CH	H	*N*-(2-aminophenyl)-3-[6-(3-phenyl-propylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.22 (bs, 1H), 8.18 (ds, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 15.4 Hz, 1H), 7.22 (m 7H), 6.90 (t, J = 7.7 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (m 3H), 4.92 (bs, 2H), 3.29 (dt, J = 7.7 Hz, 6.0 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.84 (m, J = 7.7 Hz, 2H).	3
61	95		N	CH	H	*N*-(2-aminophenyl)-3-{6-[2-(4-methoxy-phenyl)-ethylamino]-pyridin-3-yl}-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.13 (m, 1H), 6.91 (m, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.57 (m 3H), 4.92 (bs, 2H), 3.71 (s, 3H), 3.47 (dd, J = 7.3 Hz, 6.0 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H).	3
62	96		N	CH	H	*N*-(2-aminophenyl)-3-[6-(4-dimethylamino-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.23 (bs, 1H), 8.18 (bs, 1H), 7.63 (d, J= 8.2 Hz, 1H), 7.41 (m 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H).	3

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
63	97		N	CH	H	*N*-(2-aminophenyl)-3-[6-(3-imidazol-1-yl-propylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (CD_3OD-*d4*),** δ (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.98 (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H).	3
64	98		N	CH	H	*N*-(2-aminophenyl)-3-[6-(3-trifluoromethoxy-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (acetone-*d6*),** δ (ppm): 8.75 (bs, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 15.4 Hz, 1H), 7.43 (m, 2H), 7.34 (bs, 2H), 7.19 (d, J = 6.6 Hz, 1H), 6.93 (m, 2H), 6.83 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (m, 3H), 4.71 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H).	3
65	99		N	CH	H	*N*-(2-aminophenyl)-3-[6-(4-trifluoromethoxy-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (acetone-*d6*),** δ (ppm): 8.81 (bs, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.93 (m, 2H), 6.73 (m, 3H), 4.67 (d, J = 6.0 Hz, 2H), 4.66 (bs, 2H).	3

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
66	100		N	CH	H	*N*-(2-aminophenyl)-3-[6-(3,5-difluoro-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.25 (bs, 1H), 8.18 (d, J = 2.2 Hz, 1H), 7.67 (m, 2H), 7.42 (d, J = 15.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.08 (dt, J = 9.3 Hz, 2.2 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 1.9 Hz, 2H), 6.90 (dt, J = 7.3 Hz, 1.4 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.92 (bs, 2H), 4.56 (d, J = 6.0 Hz, 2H).	3
67	101		N	CH	H	*N*-(2-aminophenyl)-3-[6-(3-trifluoromethyl-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.25 (bs, 1H), 8.14 (bs, 1H), 7.86 (m, 6H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.90 (dt, J = 8.8 Hz, 1.1 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.96 (bs, 2H), 4.63 (d, J = 5.8 Hz, 2H).	3
68	102		N	CH	H	3-[6-(3-aminomethyl-benzylamino)-pyridin-3-yl]-*N*-(2-aminophenyl)--acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.28 (bs, 1H), 8.17 (bs, 1H), 7.66 (d, J = 5.8 Hz, 2H), 7.37 (m, 6H), 6.88 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.59 (m 3H), 4.55 (d, J = 5.8 Hz, 2H), 3.96 (s, 2H), 3.37 (bs, 4H).	3

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
70	104		CH	CH	H	{4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester	^{1}H NMR: (DMSO-d6) δ (ppm): 9.36 (s, 1H), 8.57 (s, 1H), 8.51 (d, J = 4.6 Hz, 1H), 7.91 (m, 1H), 7.77 (d, J = 7.68 Hz, 1H), 7.28-7.57 (m, 7H), 6.88 (dd, J = 15.66 Hz, 4.4 0 Hz, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.01 (s, 2H), 4.93 (bs, 2H), 4.10 (d, J = 6.04 Hz, 2H).	4
71	105		CH	CH	H	(2-{4-[2-(2-amino-phenylcarbamoyl)-vinyl]-phenyl}-ethyl)-carbamic acid pyridin-3-yl methyl ester	^{1}H NMR: (DMSO-d6) δ (ppm): 9.34 (s, 1H), 8.52 (m, 2H), 7.71 (d, J = 7.69 Hz, 1H), 7.20-7.60 (m, 8H), 6.87 (m, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.03 (s, 2H), 4.92 (s, 2H), 3.30 (m, 2H), 2.75 (m, 2H).	4
72	106		CH	CH	H	*N*-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (acetone-*d6*), δ (ppm): 8.49 (bs, 1H), 8.41 (d, J = 7 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.07 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 6.76 (m, 1H), 6.74 (m, 1H), 5.99 (s, 2H), 4.36 (s, 2H), 3.69 (s, 6H), 3.68 (bs, 2H), 3.67 (s, 3H).	5

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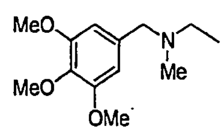
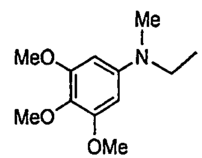
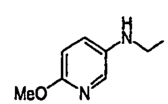
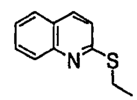
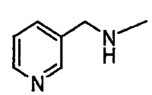
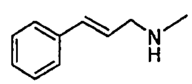
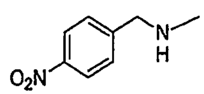
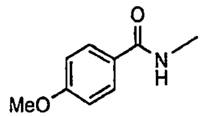
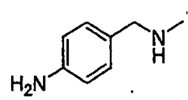
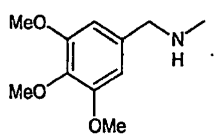
Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
73	107		CH	CH	H	*N*-(2-aminophenyl)-3-(4-{[(3,4,5-trimethoxy-benzyl)-amino]-methyl}-pheyl)-acrylamide	**^{1}H-NMR ($CDCl_3$)**, δ (ppm): 7.70 (bs, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 4.9 Hz, 2H), 7.26 (d, *J* = 4.9 Hz, 2H), 7.25 (m, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.75 (m, 1H), 6.61 (s, 2H), 6.57 (m, 1H), 4.08 (bs, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.50 (s, 2H), 3.47 (s, 2H), 2.21 (s, 3H).	5
74	108		CH	CH	H	*N*-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-phenyl)-amino]-methyl}-phenyl}-acrylamide	**^{1}H-NMR ($CDCl_3$)**, δ (ppm): 7.74 (d, *J* = 15.4 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.25 (m 3H), 7.06 (t, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 2H), 6.58 (d, *J* = 15.4 Hz, 1H), 5.96 (s, 2H), 4.50 (s, 2H), 3.79 (s, 6H), 3.78 (bs, 2H), 3.77 (s, 3H), 3.00 (s, 3H).	5
75	109		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(6-methoxy-pyridin-3-ylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR: ($DMSO-d_6$)** δ (ppm): 9.4 (bs, 1H), 7.60(d, *J* = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, *J* = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).	5

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
76	110		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(quinolin-2-ylsulfanylmethyl)-phenyl]-acrylamide	^{1}H NMR: (DMSO-d_6) δ (ppm): 9.41 (bs, 1H), 8.21 (d, J = 8.5, 1H), 7.97 (dt, J = 7.7, 8.8 Hz, 2H), 7.78 (dt, J = 7.1 Hz, 8.2 Hz, 1H), 7.61-7.53 (m, 5H), 7.40 (dd, J = 8.5 Hz, 7.6 Hz, 2H), 6.97-6.77 (m, 4H), 6.6 (dt, J = 7.7 Hz, 7.5 Hz, 1H), 4.98 (bs, 2H), 4.65 (bs, 2H).	5
77	111		CH	CH	H	*N*-(2-amino-phenyl)-3-{4-[(pyridin-3-ylmethyl)-amino]-phenyl}-acrylamide	^{1}H NMR: (DMSO-d6) δ (ppm): 9.15 (s, 1H), 7.24 -7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).	6
78	112		N	CH	H	*N*-(2-Amino-phenyl)-3-(6-styrylamino-pyridin-3-yl)-acrylamide	^{1}H NMR: (DMSO-d_6) δ (ppm): 7.96 (d, J=9.1 Hz, 2H), 7.55 (d, J = 14.2 Hz, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.39-7.29 (m, 4H), 7.07-6.91 (m, 3H), 6.81-6.64 (m, 3H), 6.47-6.38 (m, 1H), 4.21 (bs, 2H).	7
79	113		N	N	H	*N*-(2-amino-phenyl)-3-[2-(4-nitro-benzylamino)-pyrimidin-5-yl]-acrylamide	^{1}H NMR: (DMSO-d6) δ (ppm): 9.30 (s, 1H), 8.58 (bs, 2H), 8.36 (m, 1H), 8.20 (m, 2H), 7.58 (m, 2H), 7.28-7.42 (m, 2H), 6.52 -6.92 (m, 4H), 4.90 (s, 2H), 4.64 (d, J = 6 Hz, 2H).	7

Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
80	114		N	CH	H	*N*-(5-[2-(2-Amino-phenylcarbamoyl-vinyl)-pyridin-2-yl)-4-methoxy-benzamide	^{1}H NMR: (DMSO-d_6) δ (ppm): 10.87 (bs, 1H), 9.45 (bs, 1H), 8.66 (bs, 1H), 8.33 (d, J = 7.4 Hz, 1H), 8.14-8.08 (m, 3H), 7.63 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 6.8 Hz, 2H), 6.97 (d, J = 12.3 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.7 Hz, 7.4Hz, 1H), 5.06 (bs, 2H), 3.88 (s, 3H)	7
81	115		N	N	H	3-[2-(4-amino-benzylamino)-pyrimidin-5-yl]-*N*-(2-amino-phenyl)-acrylamide	^{1}H NMR: (DMSO-d6) δ (ppm): 9.27 (s, 1H), 8.83 (s, 2H), 7.97 (t, J = 6 Hz, 1H), 7.37 (d, J = 15.9 Hz, 1H), 7.29 (d , J = 7.11 Hz, 1H), 6.96 (d, J = 8.24 Hz, 2 H), 6.88 (m, 1H), 6.70 (m, 2 H), 6.55 (m, 1H), 6.47 (d, J = 8.2 Hz, 2H), 4.90 (s, 4H), 4.34 (d, J = 6.0 Hz, 2H).	7
82	116		N	CH	H	*N*-(2-aminophenyl)-3-[6-(3,4,5-trimethoxy-benzylamino)-pyridin-3-yl]-acrylamide	^{1}H-NMR ($CDCl_3$), δ (ppm): 8.38 (bs, 1H), 7.49 (m, 1H), 7.42 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.41 (m, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.10 (bs, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 15.0 Hz, 1H), 6.73 (m 1H), 6.65 (m, 2H), 6.36 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 15.0 Hz, 1H), 4.34 (s, 2H and bs, 2H), 3.84 (s, 3H), 3.81 (s, 6H).	7, 3

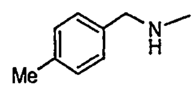
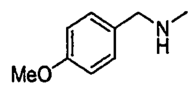
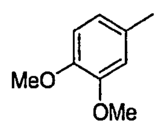
Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
83	117		N	CH	H	*N*-(2-Amino-phenyl)-3-[6-(4-methyl-benzylamino)-pyridin-3-yl]-acrylamide	**^{1}H NMR: (DMSO-d$_6$)** δ (ppm): 8.28 (bs, 1H), 7.98 (d, J = 9.6 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.08 (dt, J = 8.2 Hz, 7.7 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 6.87 (t, J = 8.2 Hz, 1H), 6.75 (d, J = 15.1 Hz, 1H), 4.57 (s, 2H), 2.53 (s, 3H).	7
84	118		N	N	H	*N*-(2-amino-phenyl)-3-[2(4-methoxy-benzylamino)-pyrimidin-5-yl]-acrylamide	**^{1}H NMR: (DMSO-d6)** δ (ppm): 9.27 (s, 1H), 8.54 (s, 2H), 8.12 (m, 1H), 7.30 (m, 4H), 6.53-6.91 (m, 6H), 4.90 (s, 2H), 4.46 (d, J = 4.9 Hz, 2H), 3.7 (s, 3H).	7
84b	118b		N	CH	H	*N*-(2-Amino-phenyl)-3-[6-(3,4-dimethoxy-phenyl)-pyridin-3-yl]-acrylamide	**^{1}H NMR (20% CD$_3$OD in CDCl$_3$):** □□8.75 (s, 1H), 7.95 (m, 1H), 7.74-7.59 (m, 3H), 7.50 (m, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.07 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.89-6.83 (m, 3H), 3.96 (s, 3H), 3.91 (s, 3H).	9, 15

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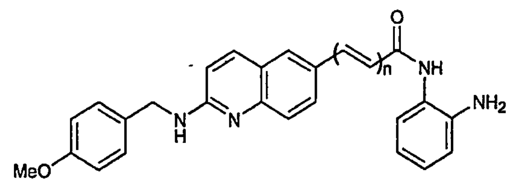
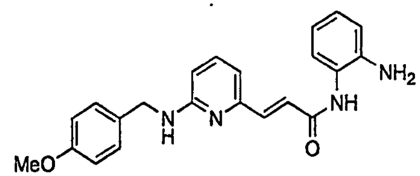
Table 3b



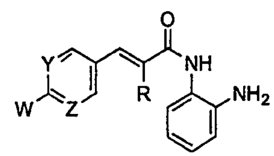
Ex.	Cpd.	n	Name	Characterization	Scheme
53	87	0	2-(4-methoxy-benzylamino)-quinoline-6-carboxylic acid (2-aminophenyl)-amide	^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H).	10
54	88	1	*N*-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide	^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H).	10

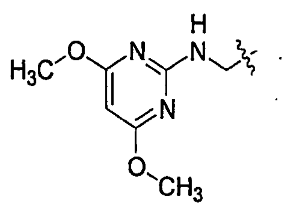
Table 3c

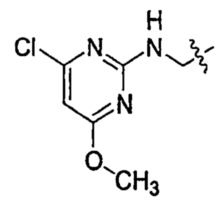
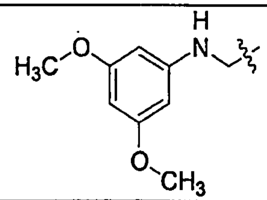
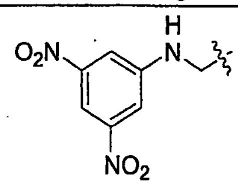
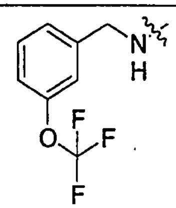
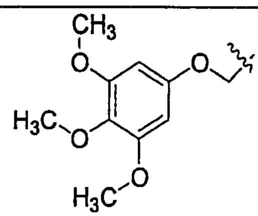


Ex.	Cpd.	Name	Characterization	Scheme
43	51	*N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide	**^{1}H-NMR ($CDCl_3$)**, δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H).	3

Table 3d



Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
347	492		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(4,6-dimethoxy-pyrimidin-2-ylamino)-methyl]-phenyl}-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.36 (bs, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.48 (s, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.33 (d J=7.9 Hz, 1H), 6.91 (m, 2H), 6.73 (d, J=8.2 Hz, 1H), 6.56 (dd, J = 7.4, 7.7 Hz, 1H), 5.35 (s, 1H), 4.93 (bs, 2H), 4.46 (dd, J=6.04 2H), 3.32 (s, 6H)	3, 7

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
348	493		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-chloro-6-methoxy-pyrimidin-2-ylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.37 (bs, 1H), 7.58-7.50 (m, 3H), 7.37-7.32 (m, 3 H), 6.94-6.83 (m, 2H), 6.75 (d J=8.0 Hz, 1H), 6.57 (t, J=7.5, 1H), 6.13 (bs , 1H), 4.94 (bs, 2H), 4.48 (d, J=6.0 , 2H), 3.84 (s, 3H)	3, 7
349	494		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(3,5-dimethoxy-benzylamino)-phenyl]-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.38 (bs, 1H), 7.55-7.40 (m, 6H), 6.88-6.57 (m, 3 H), 6.35-6.32 (m, 1H), 5.73 (m, 3H), 4.94 (s, 2 H), 4.26 (s , 2H), 3.63 (s, 6H).	3, 7
350	495		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(3,5-dinitro-benzylamino)-phenyl]-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.38 (bs, 1H), 7.74 (bs, 3H), 7.61 (d, J=8.2 Hz, 2 H), 7.56-7.44 (m, 3H), 7.32 (d J=8.0 Hz, 1H), 6.91-6.85 (m, 2H), 6.73 (d , J=7.9 Hz, 1H), 6.66-6.56 (m, 1H), 4.93 (bs, 2H), 4.52 (bs, 2H).	3, 7
351	496		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(3-trifluoromethoxy-benzylamino)-phenyl]-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.22 (bs, 1H), 7.52 (d, J=7.9 Hz, 2H), 7.44 (bs, 1H), 7.38 (bs, 3H), 7.28 (d J=6.9 Hz, 2H), 6.95-6.92 (m, 2H), 6.79 (d , J=8.2 Hz, 1H), 6.69-6.59 (m, 3H), 4.95 (bs, 2H), 4.45 (bs, 2H).	58
352	497		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxy-phenoxymethyl)-phenyl]-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.45 (bs, 1H), 8.01 (bs, 2H), 7.78-7.5 (m, 4H), 7.49-7.40 (m, 1H), 6.98 (dd, J=7.0, 8.2 Hz, 1H), 6.82 (d, J=7.0 Hz, 1H), 6.64 (dd , J=7.0, 7.6 Hz, 1H), 6.41 (bs, 2H), 5.17 (s, 2H), 3.81 (s, 6H), 3.64 (s, 3H).	3, 7

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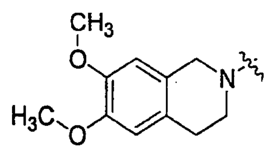
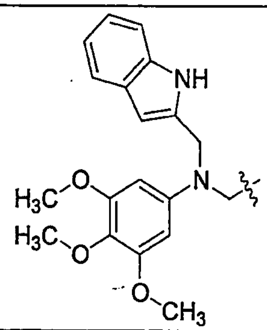
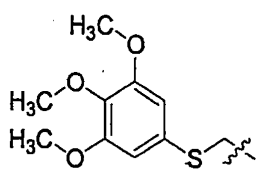
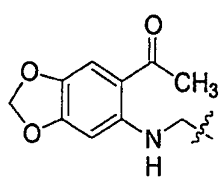
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
353	498		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.22 (bs, 1H), 7.17 (d, J=8.2 Hz, 2H), 6.97 (d, J=8.2 Hz, 2H), 6.93 (d, J=7.6 Hz, 1H), 6.85 (bs, 1H), 6.77 (bs, 1H), 6.60-6.53 (m, 3H), 6.43-6.40 (m, 2H), 4.97 (bs, 2H), 4.43 (bs, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.87-2.85 (m, 2H), 2.65-2.62 (m, 2H).	37
354	499		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[(1H-indol-2-ylmethyl)-(3,4,5-trimethoxy-phenyl)-amino]-methyl}-phenyl)-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 10.77 (bs, 1H), 9.39 (bs, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.49 (d, J=5.7 Hz, 2H), 7.37 (d, J=7.9 Hz, 2H), 7.26 (d, J=7.9, 2H), 7.10 (t, J=7.5 Hz, 2H), 7.00-6.83 (m, 4H), 6.78 (d, J=7.9 Hz, 1H), 6.61 (t, J=7.5 Hz, 1H), 5.98 (s, 1H), 5.32 (bs, 1H), 4.98 (bs, 2H), 4.32 (d, J=5.2 Hz, 2H), 3.98 (bs, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H).	58
355	500		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxy-phenylsulfanylmethyl)-phenyl]-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.69 (bs, 1H), 8.04 (d, J=8.3 Hz, 2H), 7.78 (d, J=8.3 Hz, 2H), 7.58-7.55 (m, 2H), 7.06 (d, J=6.2 Hz, 1H), 6.96 (d, J=7.3 Hz, 1H), 6.90 (d , J=7.0 Hz, 1H), 6.60 (bs, 1H), 5.81 (s, 2H), 4.34 (bs, 2H), 3.78 (s, 6H), 3.67 (s, 3H).	3, 7
356	501		CH	CH	H	3-{4-[(6-Acetyl-benzo[1,3]dioxol-5-ylamino)-methyl]-phenyl}-*N*-(2-amino-phenyl)-acrylamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.81 (bs, 1H), 7.95 (d, J=7.9 Hz, 2H), 7.58 (d, J=7.9 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4Hz, 1H), 7.02-7.00 (m, 2H), 6.85 (d, J= 7.5 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.60 (bs, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.60 (bs, 2H), 2.50 (bs, 3H).	58

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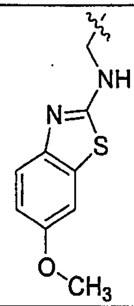
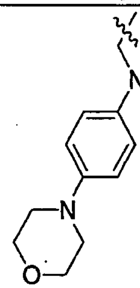
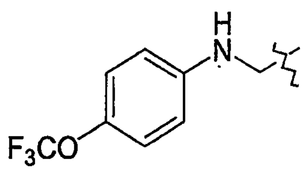
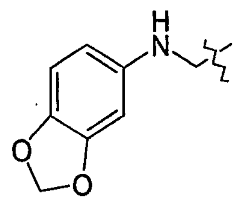
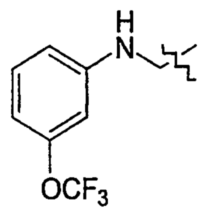
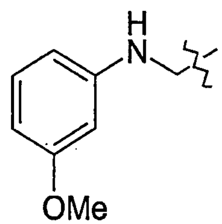
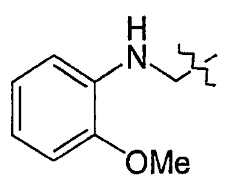
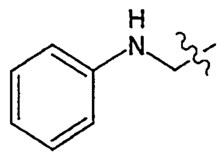
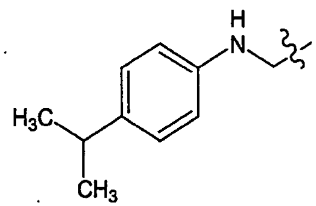
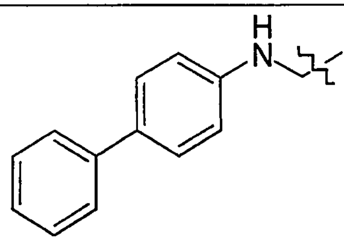
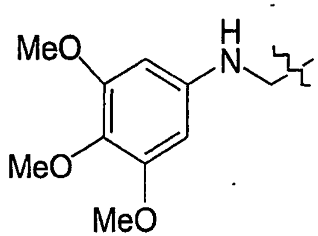
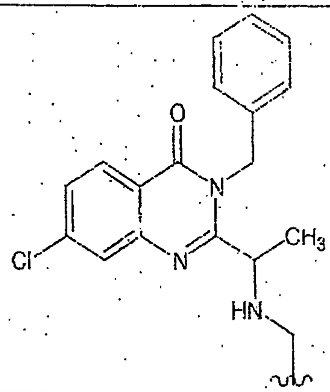
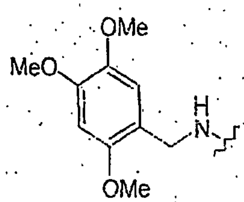
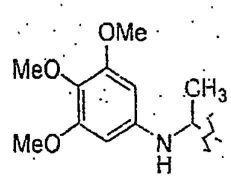
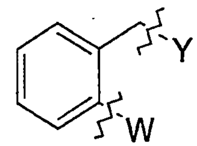
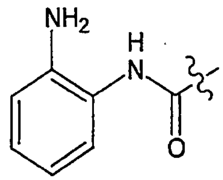
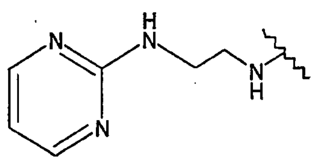
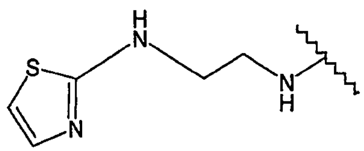
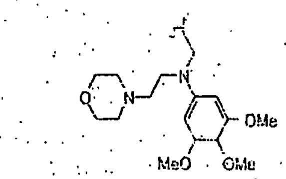
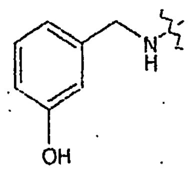
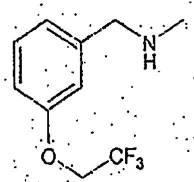
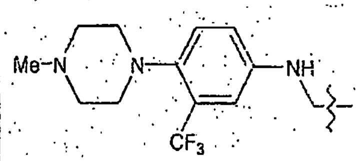
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
357	502		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(5-methoxy-benzothiazol-2-ylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.43 (bs, 1H), 8.37 (bs, 1H), 7.66-7.57 (m, 3H), 7.49 (d, J=7.5 Hz, 2H), 7.37-7.33 (m, 3H), 6.96-6.90 (m, 1H), 6.87 (d, J= 8.8 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.63 (t, J=7.5 Hz, 1H), 4.99 (bs, 2H), 4.64 (bs, 2H), 3.37 (s, 3H).	58
358	503		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-morpholin-4-yl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.42 (bs, 1H), 7.63-7.56 (m, 3H), 7.47 (d, J=7.9 Hz, 2H), 7.39 (d, J=7.5 Hz, 1H), 6.95 (d, J=8.3 Hz, 1H), 6.82 (bs, 1H), 6.77 (d, J=8.4 Hz, 2H), 6.66-6.56 (m, 3H), 5.91 (bs, 1H), 5.01 (bs, 2H), 4.30 (bs, 2H), 3.74 (bs, 4H), 2.93 (bs, 4H).	58
359	504		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(4-trifluoromethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (DMSO-*d$_6$*)**, δ (ppm): 9.42 (s, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 15.9 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.39 (d J=7.4 Hz, 1H), 7.10 (d, J = 8.2 Hz, 2H), 6.99 (d, J=7.1 Hz, 1H), 6.92 (d, J = 15.4 Hz, 1H), 6.81 (dd, J = 1.3, 8.0 Hz, 1H), 6.61-6.68 (m, 4H), 4.99 (s, 2H), 4.36 (d, J=6.0 Hz, 2H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
360	505		CH	CH	H	N-(2-Amino-phenyl)-3-[4-(benzo[1,3]dioxol-5-ylaminomethyl)-phenyl]-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.59 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.92 (d, J=16.2 Hz, 1H), 6.81 (dd, J = 1.4, 8.0 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 1.4, 7.7 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.05 (m, 2H), 5.87 (s, 2H), 4.99 (s, 2H), 4.29 (d, J=6.0 Hz, 2H).	3, 33
361	506		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(3-trifluoromethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 3H), 7.48 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 8.2, 8.2 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.93 (d, J=15.2 Hz, 1H), 6.81 (m, 2H), 6.64 (m, 2H), 6.49-6.55 (m, 2H), 5.00 (s, 2H), 4.38 (d, J= 5.3 Hz, 2H).	3, 33
362	507		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(3-methoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.90-7.02 (m, 3H), 6.81 (d, J=7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.0 Hz, 1H), 6.36 (m, 1H), 6.24 (d, J = 8.2 Hz, 1H), 6.18 (m, 2H), 5.00 (s, 2H), 4.34 (d, J= 5.3 Hz, 2H), 3.69 (s, 3H).	3, 33
363	508		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(2-methoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.58 (d, J = 15.2 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.0 Hz, 1H), 6.94-7.00 (m, 1H), 6.87 (d, J=7.6 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 7.6, 7.6 Hz, 1H), 6.56-6.66 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.68 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.41 (d, J = 6.4 Hz, 2H), 3.87 (s, 3H).	3, 33

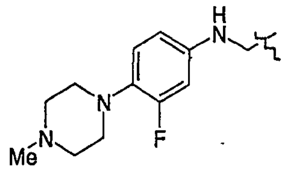
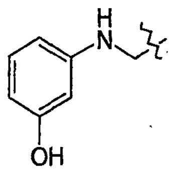
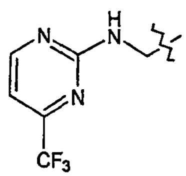
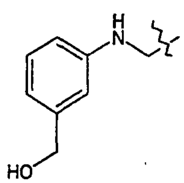
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
364	509		CH	CH	H	N-(2-Amino-phenyl)-3-(4-phenylaminomethyl-phenyl)-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.48 (d, J=7.9 Hz, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.10 (2d, J = 7.5, 7.5 Hz, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.55-6.64 (m, 4H), 6.32 (t, J = 6.0, 1H), 4.99 (s, 2H), 4.35 (d, J = 5.7 Hz, 2H).	3, 33
365	510		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(4-isopropyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.89-6.99 (m, 4H), 6.81 (d, J=7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.6 Hz, 1H), 6.56 (d, J = 8.2Hz, 2H), 6.14 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.32 (d, J= 5.9 Hz, 2H), 2.76 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H).	3, 33
366	511		CH	CH	H	N-(2-Amino-phenyl)-3-[4-(biphenyl-4-ylaminomethyl)-phenyl]-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 5H), 7.40-7.52 (m, 7H), 7.27 (dd, J = 7.0, 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.93 (d, J=15.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2Hz, 2H), 6.64 (dd, J = 7.6 Hz, 1H), 6.56 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.12 (d, J= 5.9 Hz, 2H).	3, 33
367	512		CH	N	H	N-(2-Amino-phenyl)-3-{6-[(3,4,5-trimethoxy-phenylamino)-methyl]-pyridin-3-yl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.50 (s, 1H), 8.81 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 15.7 Hz, 1H), 7.52 (d, J=8.2 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 6.96-7.05 (m, 2H), 6.81 (d, J = 8.0Hz, 1H), 6.64 (dd, J = 7.4, 7.4 Hz, 1H), 6.26 (m, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 6H), 3.56 (s, 3H).	3, 33

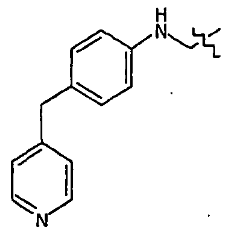
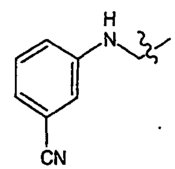
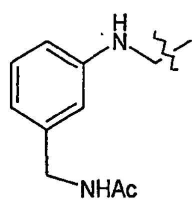
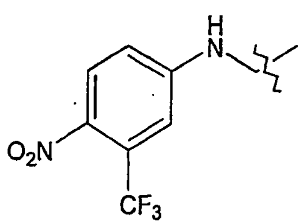
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
369	514		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-ethylamino]-methyl}-phenyl)-acrylamide	^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.50 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.81-7.72 (s, 3H), 7.66 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.45-7.26 (m, 4H), 7.24-7.15 (m, 2H), 7.00-6.86 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.68 (t, J = 7.5 Hz, 1H), 5.45 (d, J = 16.8 Hz, 1H), .533 (d, J = 16.8 Hz, 1H), 4.62 (bs, 1H), 4.25 (d, J = 12.9 Hz, 1H), 4.92 (d, J= 12.9 Hz, 1H), 1.91 (m, 2H), 1.28 (m, 1H), 0.90 (m, 1H), 0.72 (t, J = 7.5 Hz, 3H).	55
371	516	Br-	CH	CH	CH	*N*-(2-Amino-phenyl)-3-(4-bromo-phenyl)-acrylamide	^{1}H NMR: (Acetone-d_6) δ (ppm): 9.47 (bs, 1H), 7.72-7.56 (m, 5H), 7.39 (d, J=7.4 Hz, 1H), 7.00-6.95 (m, 2H), 6.81 (d, J=6.9 Hz, 1H), 6.64 (t, J=7.1 Hz, 1H), 5.00 (bs, 2H).	14
372	517		CH	CH	CH	*N*-(2-Amino-phenyl)-4-(2,4,5-trimethoxy-benzylamino)-benzamide	^{1}H NMR: (CD_3OD) δ (ppm): 7.61 (d, J=15.4 Hz, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.25 (d, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.00 (s, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.81 (t, J=7.0 Hz, 1H), 6.76 (s, 1H) 6.70 (d, J=8.4 Hz, 2H), 6.92 (d, J=15.4 Hz, 1H), 4.35 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.77 (s, 3H).	1,7, 10
373	518		CH	CH	CH	*N*-(2-Amino-phenyl)-3-{4-[1-(3,4,5-trimethoxy-phenylamino)-ethyl]-phenyl}-acrylamide	1H NMR (DMSO-*d6*) δ(ppm): 9.24 (s, 1H), 8.00 1(d, J=12Hz, 1H); 7.80 (d, J=12Hz, 1H), 7.40-7.70 (m, 7H), 6.80-7.00 (m, 2H), 6.70 (d, J = 12Hz,1H), 6.20 (s, 2H), 4.50 (m, 1H), 3.70 (s, 6H), 3.50 (s, 3H), 1.50 (d, 3H).	58

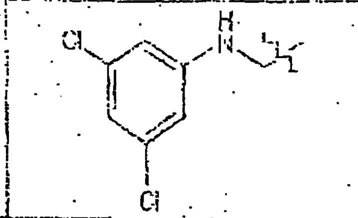
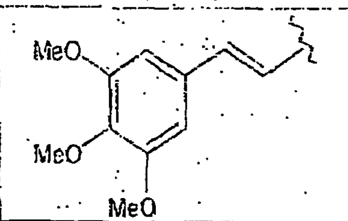
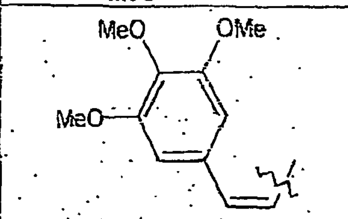
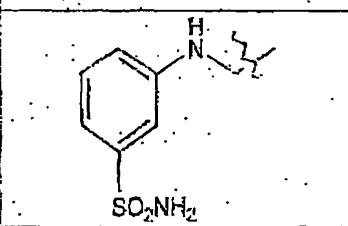
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
374	519		C	CH	H	*N*-(2-Amino-phenyl)-3-(9H-fluoren-2-yl)-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.41 (s, 1H), 8.00 (t, *J* = 7.9 Hz, 2H), 7.88 (s, 1H), 7.77-7.56 (m, 3H), 7.52-7.32 (m, 3H), 7.00 (d, *J* = 15.8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.63 (t, *J* = 7.5 Hz, 1H), 5.00 (s, 2H), 4.03 (s, 2H).	59
375	520		CH	CH	H	*N*-(2-Amino-phenyl)-4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.71 (s, 1H), 9.43 (s, 1H), AB system (δ_A = 8.05, δ_B = 7.75, *J* = 7.9 Hz, 4H), 7.62 (d, *J* = 15.8 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.05-6.88 (m, 3H), 6.78 (t, *J* = 7.9 Hz, 2H), 6.65-6.55 (m, 2H), 4.96 and 4.92 (2s, 4H).	59
376	521		N	CH	H	*N*-(2-Amino-phenyl)-3-{6-[2-(pyrimidin-2-ylamino)-ethylamino]-pyridin-3-yl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.29 (s, 1H), 8.32 (d, *J* = 4.9 Hz, 2H), 8.24 (d, *J* = 1.9 Hz, 1H), 7.71 (d, *J* = 6.9 Hz, 1H), 7.48 (d, *J* = 15.7 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.26 (bs, 2H), 6.96 (t, *J* = 6.9 Hz, 1H), 6.80 (dd, *J* = 1.1, 7.7 Hz, 1H), 6.69-6.61 (m, 4H), 5.00 (s, 2H), 3.52 (bs, 4H),	3
377	522		N	CH	H	*N*-(2-Amino-phenyl)-3-{6-[2-(thiazol-2-ylamino)-ethylamino]-pyridin-3-yl}-acrylamide	^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 8.12 (s, 1H), 8.08 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 15.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 15.4 Hz, 1H), 6.65 (s, 1H), 4.90 (s, 5H), 3.50-3.45 (m, 4H), 3.30 (d, *J* = 1.3 Hz, 1H).	3

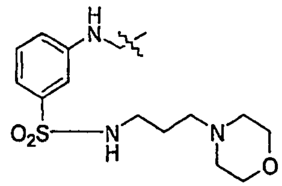
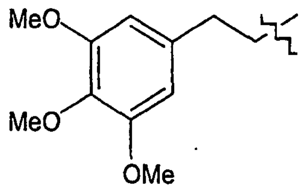
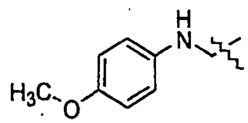
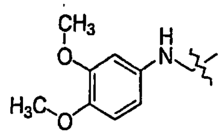
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
378	523		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[(2-morpholin-4-yl-ethyl)-(3,4,5-trimethoxy-phenyl)-amino]-methyl}-phenyl)-acrylamide	^{1}H-NMR (CD_3OD), δ (ppm): 7.83 (d, J = 15.6 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.62-7.58 (m, 2H), 7.53-7.51 (m, 2H); 7.49 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 15.6 Hz, 1H),), 4.99 (bs, 9H), 4.84 (bs, 2H), 4.22 (t, J = 6.5 Hz, 2H), 4.05 (s, 4H), 3.85 (s, 6H), 3.76 (s, 3H), 3.57-3.50 (m, 4H).	3, 33, 57
379	524		N	CH	H	*N*-(2-Amino-phenyl)-3-[6-(3-hydroxy-benzylamino)-pyridin-3-yl]-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.32 (s, 1H), 9.26 (s, 1H), 8.19 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.57 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.32 (d J=7.7 Hz), 7.10 (t, J = 7.6 Hz, 1H), 6.91 (t, J=7.6 Hz, 1H), 6.75 (m, 3H), 6.59 (m, 4H), 4.98 (bs, 2H), 4.46 (d, J=5.8 Hz, 2H).	3
380	525		N	CH	H	*N*-(2-Amino-phenyl)-3-{6-[3-(2,2,2-trifluoro-ethoxy)-benzylamino]-pyridin-3-yl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.25 (s, 1H), 8.18 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.59 (t, J = 6.0 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.30 (m, 2H), 7.00 (m, 2H), 6.92 (m, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.60 (m, 3H), 4.92 (s, 2H), 4.73 (q, J = 8.8 Hz, 2H), 4.52 (d, J = 5.8 Hz, 2H).	3
381	526		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[3-hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-methyl}-phenyl)-acrylamide	^{1}H-NMR (CD_3OD), δ (ppm): 7.64 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.49 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.21 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.88-6.71 (m, 4H), 4.88 (bs, 4H), 4.34 (s, 2H), 2.86 (t, J = 4.1 Hz, 4H), 2.67 (bs, 4H), 2.41 (s, 3H).	3, 33, 58

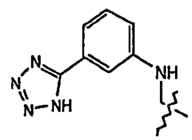
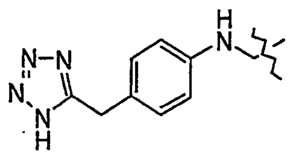
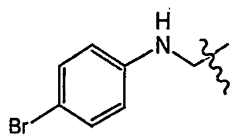
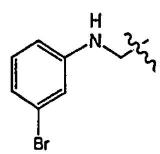
SUBSTITUTE SHEET (RULE 26)

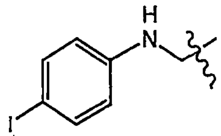
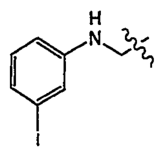
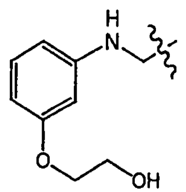
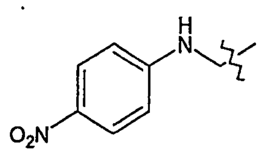
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
382	527		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[3-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamino]-methyl}-phenyl)-acrylamide	^{1}**H-NMR (DMSO-d_6,** δ (ppm): 9.43 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.00-6.88 (m, 2H), 6.85-6.79 (m, 2H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.44-6.30 (m, 3H), 4.99 (bs, 2H), 4.30 (d, *J* = 5.5 Hz, 2H), 2.87 (bs, 4H), 2.55 (m, 4H), 2.27 (s, 3H).	3, 33, 58
383	528		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-hydroxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR ($CDCl_3$),** δ (ppm): 7.49 (d, *J* = 14.0 Hz, 1H); 7.32 (d, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.05 (m, 1H), 6.96 (m, 1H), 6.90 (m, 3H), 6.76 (m, 1H), 6.55 (d, *J* = 14.0 Hz, 1H), 6.03 (m, 1H), 5.99 (m, 1H), 4.30 (bs, 5H), 4.10 (s, 2H).	3, 33
384	529		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (CD_3OD),** δ (ppm): 7.73 (d, *J* = 16.0 Hz, 1H); 7.63 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.03 (dt, *J* = 7.7, 1.4 Hz, 1H), 6.89 (d, *J* = 1.1 Hz, 1H), 6.85 (m, 1H), 6.73 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 5.27 (s, 2H), 4.87 (bs, 2H), 4.62 (s, 2H).	3, 33
385	530		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-hydroxymethyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (DMSO-d_6),** δ (ppm): 9.90 (s, 1H), 7.58 (m, 3H), 7.43 (d, *J* = 8.0 Hz, 2H); 7.37 (d, *J* = 8.0 Hz, 1H), 7.11 (m, 1H), 7.00 (m, 3H), 6.85 (d, *J* = 15.4 Hz, 1H), 6.63 (s, 1H), 6.51 (d, *J* = 7.4, Hz, 1H), 6.46 (d, *J* = 7.7 Hz, 1H), 4.35 (s, 2H), 4.32 (s, 2H).	3, 33

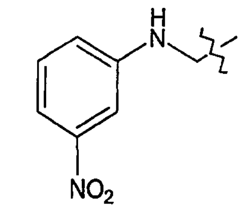
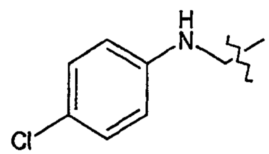
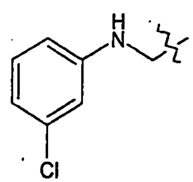
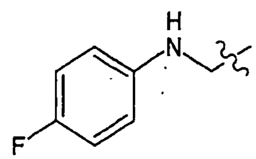
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
386	531		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-pyridin-4-ylmethyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.66 (s, 1H), 8.46 (d, J = 4.7 Hz, 2H); 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 15.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 4.7 Hz, 2H), 7.00 (d, J = 15.7 Hz, 1H), 6.92 (d, J = 6.9 Hz, 2H), 6.90 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 6.58 (m, 2H), 6.52 (d, J = 6.9, Hz, 2H), 6.10 (bs, 1H), 4.26 (bs, 2H), 3.80 (s, 2H), 2.08 (d, J = 1.9 Hz, 2H).	3, 33
387	532		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-cyano-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.38 (s, 1H), 7.58 (d, J = 7.7 Hz, 2H); 7.54 (d, J = 15.9 Hz, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 6.92-6.83 (m, 5H), 6.75 (d, J = 8.0 Hz, 1H), 6.58 (t, J = 7.4 Hz, 1H), 4.95 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H).	3, 33
388	533		CH	CH	H	3-(4-{[3-(Acetylamino-methyl)-phenylamino]-methyl}-phenyl)-N-(2-amino-phenyl)-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.37 (bs, 1H), 8.21 (t, J = 5.8 Hz, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.53 (d, J = 15.7Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.1 Hz, 1H), 6.97 (m, 1H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (dd, J = 1.4, 8.0 Hz, 1H), 6.58 (dt, J = 1.4, 8.0 Hz, 1H), 6.50 (bs, 1H), 6.41 (d, J = 8.0 Hz, 2H), 6.30 (t, J = 6.0 Hz, 1H), 4.94 (bs, 2H), 4.28 (d, J = 6.0 Hz, 2H), 4.09 (d, J = 6.0 Hz, 2H), 1.83 (s, 3H).	3, 33
389	534		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(4-nitro-3-trifluoromethyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.37 (bs, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.7Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.67-6.55 (m, 4H), 5.84 (t, J = 5.8 Hz, 1H), 4.94 (bs, 2H), 4.22 (d, J = 5.8 Hz, 2H).	3, 33

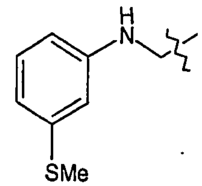
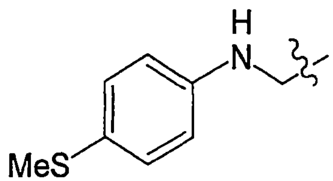
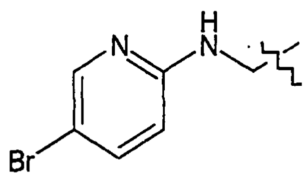
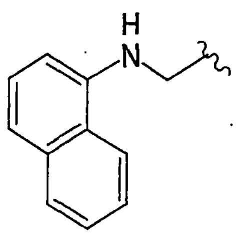
Ex.	Cpd.	W	Y	Z	R	Name	Characterization	Schm
390	535		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(3,5-dichloro-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 9.39 (bs, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 15.7 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.3 Hz, 1H), 6.97-6.83 (m, 2H), 6.87 (d, J = 15.7 Hz, 1H), 6.75 (dd, J = 1.4, 8.0 Hz, 1H), 6.60-6.55 (m, 4H), 4.95 (bs, 2H), 4.33 (d, J = 6.0 Hz, 2H).	3, 33
391	536		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-phenyl}-acrylamide	^{1}H-NMR ($CDCl_3$), δ (ppm): 8.12 (bs, 1H), 7.64 (d, J = 14.2 Hz, 1H), 7.42 (bs, 4H), 7.23 (bs, 2H), 6.97 (d, J = 14.2 Hz, 1H), 6.94-6.82 (m, 4H), 6.70 (s, 2H), 4.11 (bs, 2H), 3.87 (s, 6H), 3.84 (s, 3H).	3
392	537		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-d_6), δ (ppm): 8.49 (s, 1H), 7.58 (d, J = 15.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (m, 4H), 7.00 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 5.0 Hz, 2H), 6.69 (d, J = 5.0 Hz, 2H), 6.58 (d, J = 15.4 Hz, 1H), 6.53 (bs, 2H), 6.47 (s, 2H), 3.85 (s, 3H), 3.63 (s, 6H).	3
393	538		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(3-sulfamoyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR ($CD_3OD/CDCl_3$), δ (ppm): 7.61 (d, J = 15.7 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.18 (dd, J = 8.0 Hz, 2H), 7.12 (d, J = 15.7 Hz, 1H), 7.10 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.83-6.66 (m, 4H), 3.93 (bs, all NH signals).	1, 3, 33

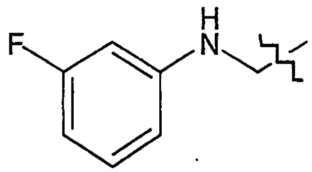
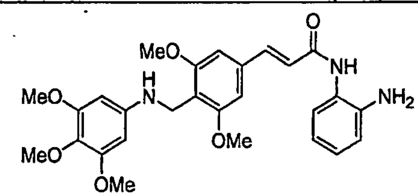
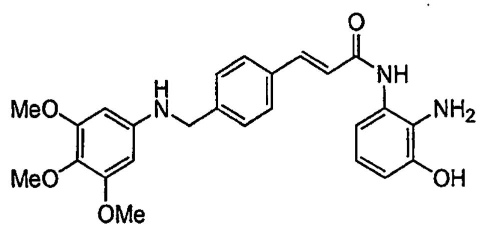
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
394	539		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[3-(3-morpholin-4-yl-propylsulfamoyl)-phenylamino]-methyl}-phenyl)-acrylamide	^{1}**H-NMR (CDCl$_3$)**, δ (ppm): 8.34 (bs, 1H), 7.64 (d, *J* = 15.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.34 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 15.4 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.04 (m, 2H), 6.74 (m, 4H), 4.85 (bs, 1H), 4.30 (d, *J* = 4.4 Hz, 2H), 3.69 (t, *J* = 4.4 Hz, 4H), 2.99 (t, *J* = 5.8 Hz, 2H), 2.40 (bs, 6H), 1.59 (t, *J* = 4.4 Hz, 2H).	3, 33, 42
395	540		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[2-(3,4,5-trimethoxy-phenyl)-ethyl]-phenyl}-acrylamide	^{1}**H-NMR (CDCl$_3$)**, δ (ppm): 8.53 (s, 1H), 7.72 (d, *J* = 15.6 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.33 (m, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.07 (m, 1H), 6.79 (m, 2H), 6.69 (d, *J* = 15.6 Hz, 1H), 6.41 (s, 2H), 4.04 (bs, 2H), 3.91 (s, 3H), 3.85 (s, 6H), 2.94 (m, 4H).	3, 32
396	541		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(4-methoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (DMSO-d$_6$)**, δ (ppm): 9.35 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 15.4 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 15.4 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.58 (m, 1H), 6.52 (d, *J* = 8.6 Hz, 2H), 5.84 (t, *J* = 5.5 Hz, 1H), 4.23 (d, *J* = 5.5 Hz, 2H), 3.61 (s, 3H).	3, 33
397	542		CH	CH	H	N-(2-Amino-phenyl)-3-{4-[(3,4-dimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}**H-NMR (CDCl$_3$)**, δ (ppm): 8.48 (s, 1H), 7.60 (d, *J* = 15.4 Hz, 1H), 7.27 (m, 5H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.70 (m, 3H), 6.59 (d, *J* = 15.4 Hz, 1H), 6.25 (s, 1H), 6.12 (d, *J* = 7.1 Hz, 1H), 4.23 (s, 2H), 3.93 (bs, 3H), 3.75 (s, 3H), 3.73 (s, 3H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
398	543		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[3-(1H-tetrazol-5-yl)-phenylamino]-methyl}-phenyl)-acrylamide	**^{1}H-NMR (CD_3OD)**, δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.33 (m, 3H), 7.27 (m, 3H), 7.20 (m, 1H), 6.84 (m, 2H), 5.48 (bs, 5H), 4.46 (s, 2H).	3, 33
399	544		CH	CH	H	N-(2-Amino-phenyl)-3-(4-{[4-(1H-tetrazol-5-ylmethyl)-phenylamino]-methyl}-phenyl)-acrylamide	**^{1}H-NMR (CD_3OD)**, δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.29 (m, 2H), 7.20 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 15.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 5.48 (bs, 5H), 4.39 (s, 2H). 4.16 (s, 2H).	3, 33
400	545		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-bromo-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 15.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 15.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.66-6.57 (m, 4H), 4.99 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H).	3, 33
401	546		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-bromo-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.00-6.91 (m, 2H), 6.86 (d, J = 15.8 Hz, 1H), 6.74 (d, J = 8.2 Hz, 2H), 6.66-6.54 (m, 4H), 4.93 (bs, 2H), 4.30 (d, J = 5.3 Hz, 2H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
402	547		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-iodo-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.36 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.35 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.57 (t, J = 8.0 Hz, 1H), 6.52 (t, J = 6.0 Hz, 1H), 6.42 (d, J = 8.5 Hz, 2H), 4.94 (bs, 2H), 4.28 (d, J = 6.0 Hz, 2H).	3, 33
403	548		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-iodo-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.40 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 6.92 (m, 3H), 6.84 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.60-6.50 (m, 3H), 4.93 (bs, 2H), 4.28 (d, J = 5.9 Hz, 2H).	3, 33
404	549		CH	CH	H	*N*-(2-Amino-phenyl)-3-(4-{[3-(2-hydroxy-ethoxy)-phenylamino]-methyl}-phenyl)-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 15.3 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.03-6.98 (m, 2H), 6.91 (d, J = 15.3 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 5.9 Hz, 1H), 6.28-6.22 (m, 3H), 4.99 (bs, 3H), 4.61 (s, 2H), 4.34 (d, J = 5.0 Hz, 2H) 4.28 (d, J = 5.0 Hz, 2H).	3, 33
405	550		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-nitro-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.38(s, 1H), 7.99 (d, J = 9.1 Hz, 2H), 7.85 (t, J = 5.9 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 6.94-6.92 (m, 1H), 6.88 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 9.1 Hz, 2H), 6.58 (t, J = 7.6 Hz, 1H), 4.94 (bs, 2H), 4.46 (d, J = 5.9 Hz, 2H)	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
406	551		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-nitro-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.37 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 15.2 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.36-7.28 (m, 4H), 7.05-6.98 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 15.2 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.58 (t, *J* = 7.6 Hz, 1H), 4.96 (bs, 2H), 4.39 (d, *J* = 5.3 Hz, 2H).	3, 33
407	552		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-chloro-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.43 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 15.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 15.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.55 (bs, 2H), 4.99 (bs, 2H), 4.46 (d, *J* = 5.9 Hz, 2H), 4.35 (d, *J* = 5.9 Hz, 2H)	3, 33
408	553		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-chloro-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.50 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 15.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.43 (m, 1H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.79 (d, *J* = 15.4 Hz, 1H), 6.68 (m, 3H), 6.59 (m, 3H), 5.24 (bs, 2H), 4.31 (s, 2H).	3, 33
409	554		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-fluoro-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.37(s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 15.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.41 (m, 1H), 7.01-6.90 (m, 4H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.67-6.59 (m, 3H), 6.27 (bs, 1H), 4.95 (bs, 2H), 4.27 (s, 2H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
410	555		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-methylsulfanyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.64 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 6.37 (d, J = 7.8 Hz, 1H), 4.29 (s, 2H), 4.05 (bs, 4H), 2.37 (s, 3H).	3, 33
411	556		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-methylsulfanyl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.60-6.54 (m, 3H), 6.39 (t, J = 5.7 Hz, 1H), 4.93 (bs, 2H), 4.29 (d, J = 6.1 Hz, 2H), 2.32 (s, 3H),.	3, 33
412	557		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(5-bromo-pyridin-2-ylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.36 (s, 1H), 8.02 (d, J = 1.7 Hz, 1H), 7.57-7.50 (m, 4H), 7.38-7.32 (m, 4H), 6.92 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 16.3 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 4.94 (bs, 2H), 4.48 (d, J = 5.7 Hz, 2H).	3, 33
413	558		CH	CH	H	N-(2-Amino-phenyl)-3-[4-(naphthalen-1-ylaminomethyl)-phenyl]-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.37 (s, 1H), 8.25 (m, 1H), 7.76 (m, 1H), 7.57 (m, 2H), 7.47 (m, 4H), 7.33 (d, J = 7.0 Hz, 1H), 7.17 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.99 (t, J = 5.3 Hz, 1H), 6.92 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 16.4 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.57 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 7.6 Hz, 1H), 4.90 (s, 2H), 4.54 (d, J = 5.3 Hz, 2H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
414	559		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-fluoro-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.39 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.02 (q, J = 7.6 Hz, 1H), 6.90 (m, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (m, 1H), 6.40 (d, J = 8.2 Hz, 1H), 6.29 (m, 2H), 4.90 (s, 1H), 4.29 (bs, 2H), 4.02 (s, 2H).	3, 33
415	560					*N*-(2-Amino-phenyl)-3-{3,5-dimethoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR ($CDCl_3$), δ (ppm): 7.73 (bs, 1H), 7.63 (d, J = 14.9 Hz, 1H), 6.81 (m, 3H), 6.70 (m, 2H), 6.68-6.56 (m, 2H), 6.07 (s, 2H), 4.35 (s, 2H), 3.86 (s, 6H), 3.81 (s, 6H), 3.75 (s, 3H).	60
416	561					N-(2-Amino-3-hydroxy-phenyl)-3-{4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 9.11 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 15.8 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 15.8 Hz, 1H), 6.78 (t, J = 7.9 Hz, 1H), 6.23 (t, J = 7.9 Hz, 1H), 6.16 (d, J = 7.9 Hz, 1H), 6.09 (t, J = 6.2 Hz, 1H), 5.89 (s, 2H), 4.77 (bs, 2H), 4.27 (d, J = 5.7 Hz, 2H), 5.89 (s, 6H), 5.76 (s, 3H).	3, 33

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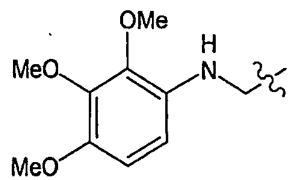
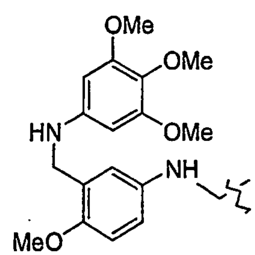
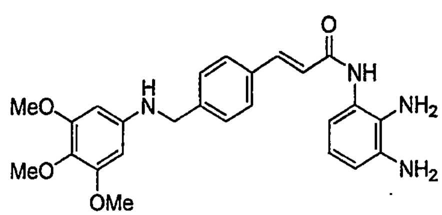
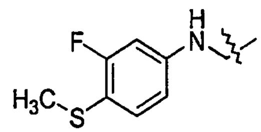
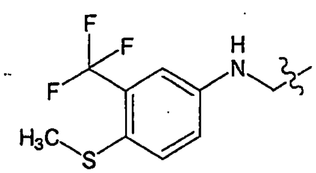
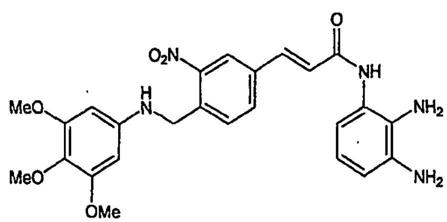
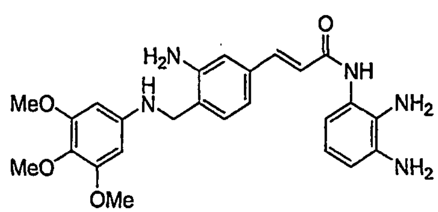
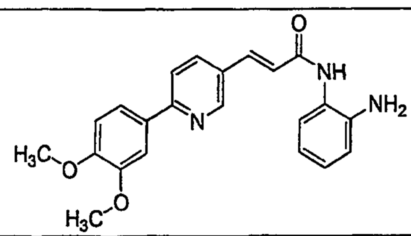
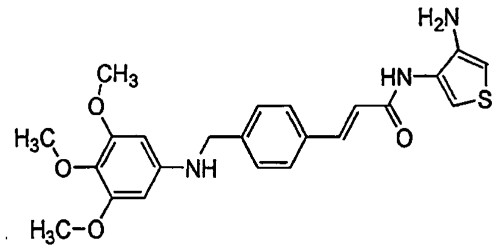
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
417	562		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(2,3,4-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H), 7.74 (d, J = 15.5 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.34-7.29 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.79 (m, 1H), 6.66 (d, J = 15.5 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 8.8 Hz, 1H), 4.36 (s, 2H), 4.18 (bs, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.84 (s, 3H).	3, 33
418	563		CH	CH	H	*N*-(2-Amino-phenyl)-3-[4-({4-methoxy-3-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenylamino}-methyl)-phenyl]-acrylamide	^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58 (s, 1H), 7.66 (d, J = 15.4 Hz, 1H), 7.33-7.28 (m, 3H), 7.23 (d, J = 7.0 Hz, 2H), 7.04 (t, J = 7.0 Hz, 1H), 6.77-6.70 (m, 4H), 6.64 (d, J = 15.4 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 5.90 (s, 2H), 4.27 (s, 2H), 4.25 (s, 2H), 4.08 (bs, 4H), 3.82 (s, 6H), 3.77 (s, 6H).	3, 33

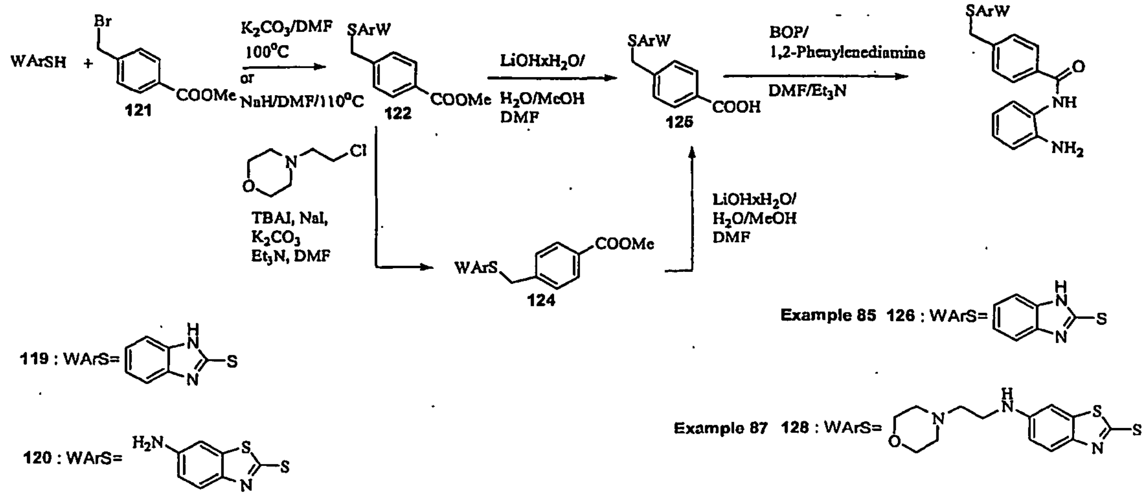
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
419	564					N-(2,3-Diamino-phenyl)-3-{4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (d, J = 15.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.31-7.24 (m, 2H), 6.86 (s, 1H), 6.73 (d, J = 15.4 Hz, 1H), 5.84 (s, 2H), 4.27 (s, 2H), 4.00 (bs, 6H), 3.71 (s, 6H), 3.68 (s, 3H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
420	565		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(3-fluoro-4-methylsulfanyl-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H-NMR (DMSO-d$_6$)**, δ (ppm): 9.38 (bs, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 15.4Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 8.3 Hz, 1H), 6.94-6.89 (m, 2H), 6.81 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.43-6.38 (m, 2H), 4.94 (bs, 2H), 4.30 (d, J = 5.7 Hz, 2H). 2.28 (s, 3H).	3, 33
421	566		CH	CH	H	*N*-(2-Amino-phenyl)-3-{4-[(4-methylsulfanyl-3-trifluoromethyl-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H-NMR (DMSO-d$_6$)**, δ (ppm): 9.39 (bs, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 15.8Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 6.2 Hz, 1H), 6.96-6.90 (m, 4H), 6.82 (d, J = 15.8Hz, 1H), 6.79-6.74 (m, 1H), 6.58 (t, J = 7.5 Hz, 1H), 4.95 (bs, 2H), 4.35 (d, J = 6.2 Hz, 2H). 2.35 (s, 3H).	3, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
42 2	567					*N*-(2-Amino-phenyl)-3-{3-nitro-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H-NMR (DMSO-d_6)**, δ (ppm): 9.50 (s, 1H), 8.09 (s, 1H), 7.80 (d, J = 15.4 Hz, 1H), 7.81 (s, 2H), 7.34 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 15.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.26 (t, J = 6.2 Hz, 1H), 5.90 (s, 2H), 4.96 (bs, 2H), 4.39 (d, J = 5.7 Hz, 2H), 3.66 (s, 6H), 3.51 (s, 3H).	3, 33
42 3	568					*N*-(2-Amino-phenyl)-3-{3-amino-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	**^{1}H-NMR (DMSO-d_6)**, δ (ppm): 9.29 (s, 1H), 7.72 (d, J = 15.4 Hz, 1H), 7.33 (m, 2H), 6.90 (1H); 6.71 (2H) , 6.62 (3H) , 5.97 (1H) , 5.87 (2H) , 5.49 (2H) , 4.96 (2H) , 4.10 (2H) , 3.65 (6H) , 3.51 (3H).	3, 33
42 4	569					*N*-(2-Amino-phenyl)-3-[6-(3,4-dimethoxy-phenyl)-pyridin-3-yl]-acrylamide	**LRMS:** calc: 375.4, found: 376.4	3, 15, 33

Ex.	Cpd	W	Y	Z	R	Name	Characterization	Schm
425	570					*N*-(4-Amino-thiophen-3-yl)-3-{4-[(4-morpholin-4-yl-phenylamino)-methyl]-phenyl}-acrylamide	^{1}H-NMR (DMSO-*d6*), δ (ppm): 9.64 (bs, 1H), 7.65 (d, J=7.9 Hz, 2H), 7.60 (d, J=14.0 Hz, 1H), 7.50 (d, J=7.9 Hz, 2H), 6.90 (d, J=15.8 Hz, 1H), 6.15 (d, J=4.0 Hz, 1H), 5.95 (s, 2H), 5.82 (s, 1H), 4.89 (bs, 2H), 4.33 (d, J=5.7 Hz, 2H), 3.71 (s, 6H), 3.57 (s, 3H).	3, 33, 60

SUBSTITUTE SHEET (RULE 26)



Example 85

N-(2-Amino-phenyl)-4-(1H-benzimidazol-2-ylsulfanylmethyl)-benzamide (compound 126)

Step 1: 4-(1H-Benzimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (compound 122)

[0215] Following the procedure described in Example 47, step 2, but using **119** and substituting **121** for **63**, the title compound **122** was obtained in 95% yield. LRMS = 299.1 (M+1).

Step 2: N-(2-Amino-phenyl)-4-(1H-benzimidazol-2-ylsulfanylmethyl)-benzamide (126)

[0216] Following the procedure described in Example 1, steps 4 and 5, but substituting **122** for **6**, the title compound **126** was obtained in 62% yield. ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.57 (s, 1H), 7.89 (d, J= 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.53 (bs, 2H), 7.36 (bs, 2H), 7.14-7.08 (m, 3H), 6.94 (t, J = 8.2 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 6.56 (t, J = 8.0 Hz, 1H), 4.87 (bs, 2H), 4.62 (s, 2H).

Example 87

N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound 128)

Step 1: 4-(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (122)

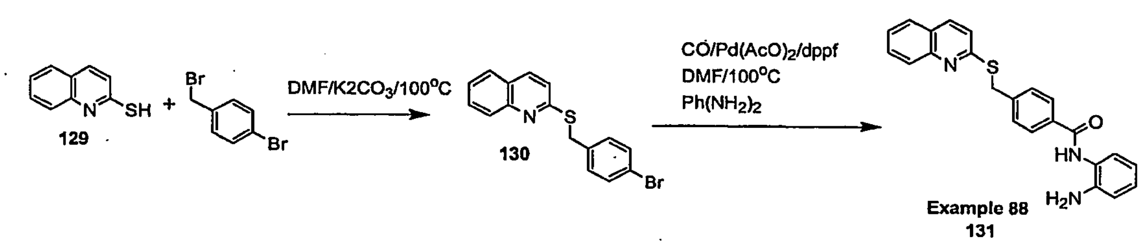
[0217] Following the procedure described in Example 47, step 2, but using **120** and substituting **121** for **63**, the title compound **122** was obtained in 45% yield. LRMS = 331.0 (M+1).

Step 2: 4-[6-(2-Morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (compound **124**)

[0218] To a solution of 4-(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester **122** (800 mg, 2.42 mmol), in DMF (24 mL), were added successively solid 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol), K_2CO_3 (611 mg, 5.08 mmol), NaI (363 mg, 2.42 mmol), Et_3N (370 µL, 2.66 mmol) and tetrabutylammonium iodide (894 mg, 2.42 mmol), The mixture was stirred at 120°C for 24h and more 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol) was added. The mixture was stirred for 8h at 120°C and the solvent was removed *in vacuo*. The resulting black syrup was partitioned between H_2O and EtOAc. The organic layer was successively washed with HCl 1N and saturated aqueous $NaHCO_3$. The precipitate was extracted twice with EtOAc, dried over $MgSO_4$ and concentrated. Purification by flash chromatography ($MeOH/CHCl_3$: 5:95 to 10:90) afforded 48 mg (4% yield) of **124** as a light yellow oil. LRMS = 444.1 (M+1).

Step 3: *N*-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound **128**)

[0219] Following the procedure described in Example 1, steps 4 and 5, but substituting **124** for **6**, the title compound **128** was obtained in 76% yield. ^{1}H NMR: (Acetone-d_6) δ (ppm): 9.06 (bs, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 7.02-6.97 (m, 1H), 6.87-6.82 (m, 2H), 6.66 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.63 (s, 2H), 3.64-3.60 (m, 4H), 3.25 (t, J = 6.3 Hz, 2H), 2.63 (t, J = 6.3 Hz, 2H), 2.54-2.42 (m, 4H).



Example 88

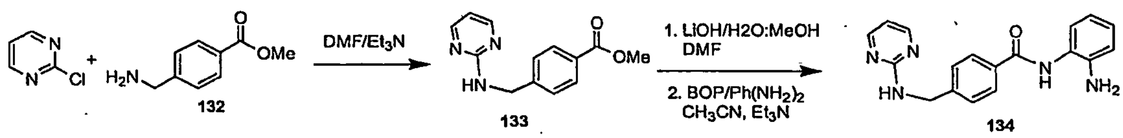
N-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (compound 131)

Step 1: 2-(4-Bromo-benzylsulfanyl)-quinoline (compound **130**)

[0220] Following the procedure described in Example 47, step 2, but substituting **129** for **63**, the title compound **130** was obtained in 89% yield. LRMS = 332.0 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (**131**)

[0221] Following the procedure described in Example 40, step 2, but substituting **129** for **42**, the title compound **131** was obtained in 70% yield. ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).



Example 89

Example 89

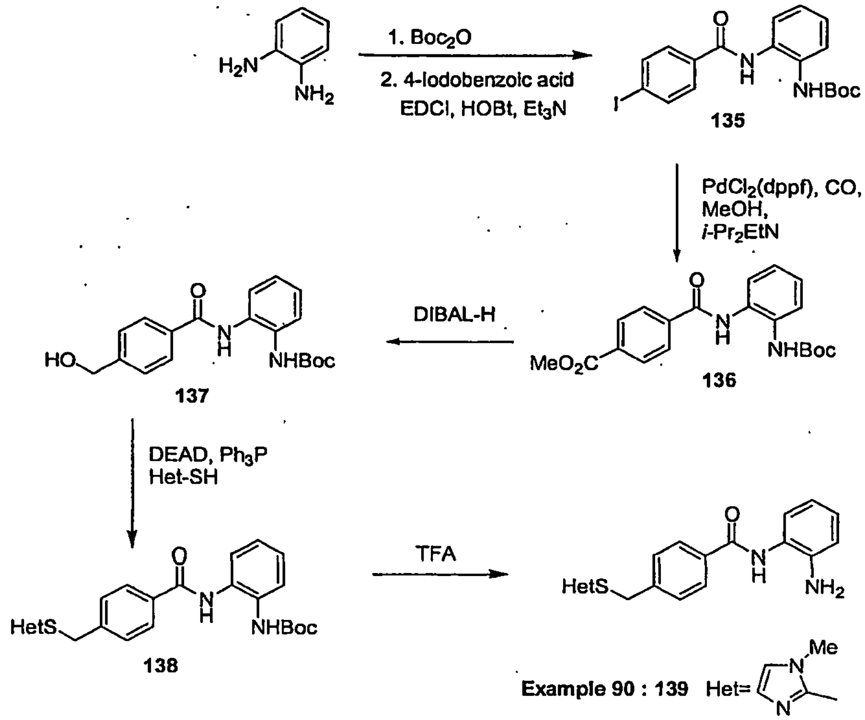
N-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (compound 134)

Step 1: 4-(Pyrimidin-2-ylaminomethyl)-benzoic acid methyl ester (compound **133**)

[0222] Following the procedure described in Example 47, step 2, but substituting **132** for **63**, the title compound **133** was obtained in 76% yield. LRMS = 244.2 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (**134**)

[0223] Following the procedure described in Example 1, steps 4 and 5, but substituting **129** for **6**, the title compound **134** was obtained in 91% yield. ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.6 (bs, 1H), 8.32 (d, J = 4.9 Hz, 2H), 7.97 (dt, J = 9.9 Hz, 7.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47, (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H).



Example 90 : 139 Het=

Example 90

***N*-(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl]-benzamide (compound 139)**

Step 1: [2-(4-Iodo-benzoylamino)-phenyl]-carbamic acid *tert*-butyl ester (compound 135)

[0224] To a solution of di-*tert*-butyldicarbonate (39 g, 181 mmol) in THF (139 mL) placed in a water bath, was added 1,2-phenylenediamine (15 g, 139 mmol) and DMAP (1.7 g, 14 mmol). The mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. The crude material was partitioned between EtOAc and water. The organic layer was washed with HCl 1 N and then with aqueous saturated $NaHCO_3$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated affording the compound (18.9 g, 65% yield) as a light beige powder. LRMS = 209.1 (M+1).

[0225] To a solution of 4-iodobenzoic acid (8.0 g, 32.3 mmol) in DMF (65 mL) at r.t., were successively added 1-[3-(dimethylamino)propyl]-3-ethylcabodiimide hydrochloride (8.0 g, 41.9 mmol) and 1-hydroxybenzotriazole (5.2 g, 38.7 mmol). The mixture was stirred for 1 h and a solution of (2-amino-phenyl)-carbamic acid *tert*-butyl ester (6.3 g, 30.2 mmol) in DMF (20 mL) was added to the mixture *via* cannula, followed by triethylamine (5.9 mL, 4.9 mmol). The mixture

was stirred for 16 h and the solvent was removed *in vacuo*. The crude material was partitioned between chloroform and water. The organic layer was washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to a light brown syrup which was crystallized in hot EtOAc or Et_2O, yielding **135** (9.3 g, 70% yield) as a white solid. LRMS = 461.0 ($M+Na^+$).

Step 2: *N*-[2-*tert*-butoxycarbonylamino-phenyl)-terephtalamic acid methyl ester (compound **136**)

[0226] Following the procedure described in Example 40, step 2, but substituting **135** for **42**, the title compound **136** was obtained in 95% yield. LRMS = 393.1 ($M+Na^+$).

Step 3: [2(4-Hydroxymethyl-benzoylamino)-phenyl]-carbamic acid *tert*-butyl ester (**137**)

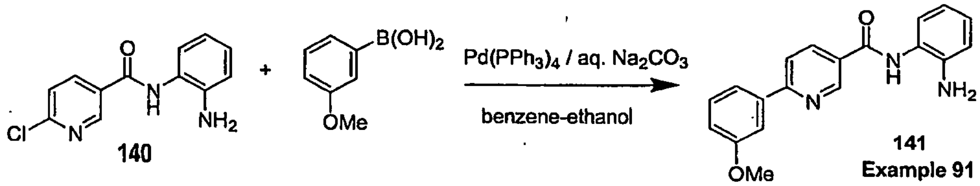
[0227] To a solution of **136** (7.5g, 20.6 mmol) in THF (40 mL), cooled down to -20°C under N_2, was added a 1M solution of DIBAL-H (122 mL, 122 mmol) in toluene. After stirring for 18 h. at r.t., the mixture was cooled down to 0°C and carefully quenched by a dropwise addition of H_2O (10 mL) and of 2N NaOH (5 mL). The aluminum salts were allowed to decant and the supernatant was removed. The organic layer was washed with H_2O, 1 N HCl (6 times), satd. aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated (2.04 g, 43%). Purification of the crude material by flash chromatography (EtOAc/hexanes 50:50 to 70:30) afforded **137** (1.14 g, 16% yield) as a solid foam. LRMS = 365.2 ($M+Na^+$).

Step 4: {2-[4-(1-Methyl-imidazol-2-ylsulfanylmethyl)-benzoylamino]-phenyl}-carbamic acid *tert*-butyl ester (compound **138**)

[0228] To a solution of *N*-methyl-2-mercaptoimidazole (28 mg, 0.25 mmol) in THF (1 mL), at r.t. under N_2 atmosphere were successively added **137** (70 mg, 0.20 mmol), triphenylphosphine (70 mg, 0.27 mmol) followed by dropwise addition of diethyl azodicarboxylate (48 μL, 0.31 mmol). The mixture was stirred for 2 h and the solvent was removed *in vacuo*. Purification by flash chromatography using $MeOH/CHCl_3$ (5:95) as the eluent afforded the title compound **138** (81 mg), in 91% yield, which was found to contain some diethyl hydrazodicarboxylate residus. The compound was used as is without further purification.

Step 5: *N*-(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl]-benzamide (compound 139)

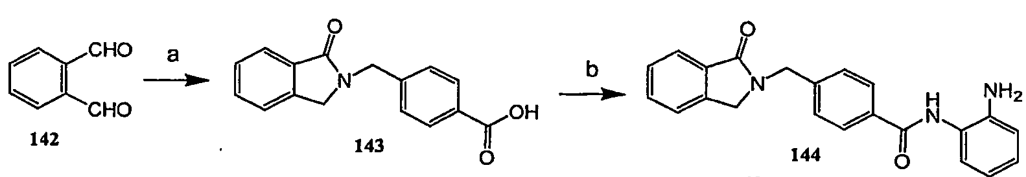
[0229] Following the procedure described in Example 42, step 3, but substituting **138** for **46**, the title compound **139** was obtained in 62% yield. ^{1}H NMR: (Acetone-d_6) δ (ppm): 9.07 (bs, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.1 Hz, 1H), 7.03-6.96 (m, 2H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 7.4 Hz, 1.1 Hz, 1H), 4.63 (bs, 2H), 4.29 (s, 2H), 3.42 (s, 3H).



Example 91

***N*-(2-Amino-phenyl)-6-(3-methoxyphenyl)-nicotinamide (compound 141)**

[0230] To a mixture of 3-methoxyphenyl boronic acid (152 mg, 1.0 mmol) and **140** (248 g, 1.0 mmol) were added benzene (8 mL) and ethanol (4 mL) followed by 2 M Na_2CO_3 aqueous solution (3.2 mL, 6.4 mmol). The reaction mixture was stirred under nitrogen for 30 min and then $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) was quickly added. After 24 h of reflux, the mixture was cooled to room temperature, filtered through a pad of celite and rinsed with ethyl acetate (30 mL). The organic solution was washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Purification by flash silica gel chromatography (Hexane/Ethyl acetate: 1/1) afforded **141** (302 mg, 95% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.11 (d, J = 1.8 Hz, 1H), 8.30 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.52-7.47 (m, 1H), 7.36 (m, 1H), 7.22 (m, 1H), 7.09-6.78 (m, 4H), 3.84 (s, 3H), 3.39 (br s, 2H).



a. p-aminomethylbenzoic acid/AcOH/5 min/reflux
b. HOBT/EDC/1,2-diamino benzene

Example 92

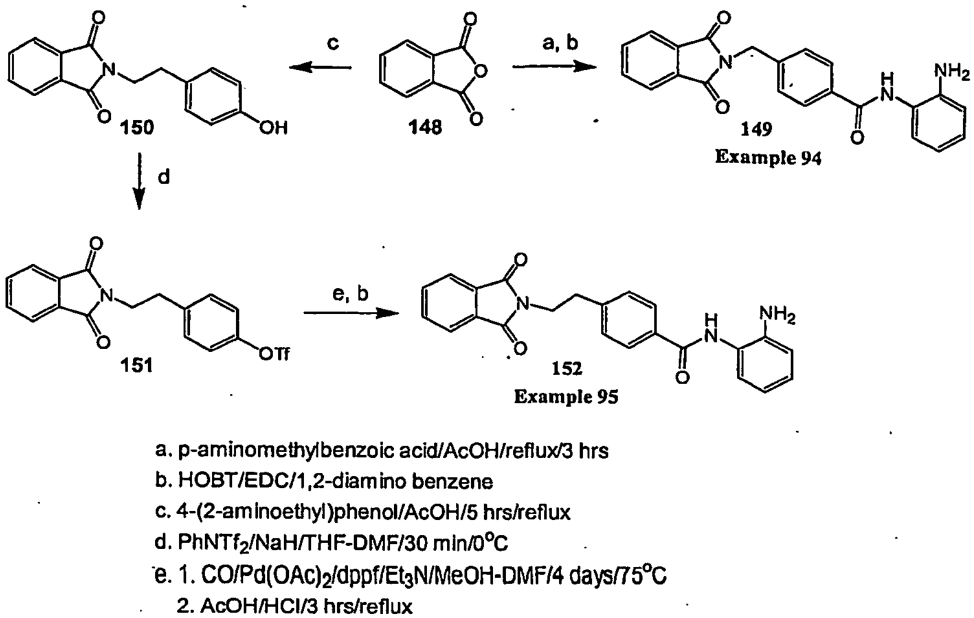
N-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 144)

Step 1: 4-(1-Oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzoic acid (compound 143)

[0231] To a solution of benzene-1,2-carbaldehyde **142** (1.0 g, 7.46 mmol) in 10 mL of acetic acid was added 4-aminomethylbenzoic acid (1.13 g, 7.46 mmol). The reaction mixture was refluxed 5 min and cooled to the room temperature. A crystalline precipitate was formed and triturated with CH_2Cl_2 to produce the title compound **143** (1.29 g, 49%).

Step 2: *N*-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound **144**)

[0232] To a solution of the carboxylic acid (0.32 g, 0.89 mmol) in DMF (8 mL) at rt, was added HOBt (0.16 g, 1.15 mmol) and EDC (0.25 g, 1.33 mmol) and the solution was stirred for 1.5 h. Lastly, phenylenediamine (0.12 g, 1.07 mmol) was added and the mixture was allowed to stir for 18-20 h. DMF was removed *in vacuo* and the crude was partitioned between ethyl acetate and H_2O. The organic layer was dried over Na_2SO_4 and concentrated. Purification by column chromatography (CH_2Cl_2-MeOH (19:1)) afforded **144** in 46% yield. ^{1}H NMR: (DMSO-d_6) □ 9.71 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.55-7.70 (m, 3H), 7.46 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H), 4.93 (bs, 2 H), 4.87 (s, 2 H), 4.47 (s, 2H).



Example 94

N-(2-Amino-phenyl)- 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 149)

[0233] Phthalic anhydride **148** (1.3 g, 8.9 mmol) and 4-aminomethylbenzoic acid in 20 mL acetic acid were refluxing for 3 h, cooled to the room temperature and evaporated to yield a solid residue which was triturated with water, filtered off and dried to produce the intermediate carboxylic acid (1.7 g, 68%). LMRS = 282.0 (M+1).

[0234] Following a procedure analogous to that described in Example 92, step 2, but substituting the acid for **143**, the title compound **149** was obtained in 17% yield. ^{1}H NMR: (DMSO d_6) □ 9.59 (s, 1H), 7.82-7.91 (m, 6H), 7.40 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.55 (t, J = 7.4 Hz, 1H), 4.83 (bs, 4H).

Example 95

N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)

<u>Step 1: 2-[2-(4-Hydroxy-phenyl)-ethyl]-isoindole-1,3-dione (compound 150)</u>

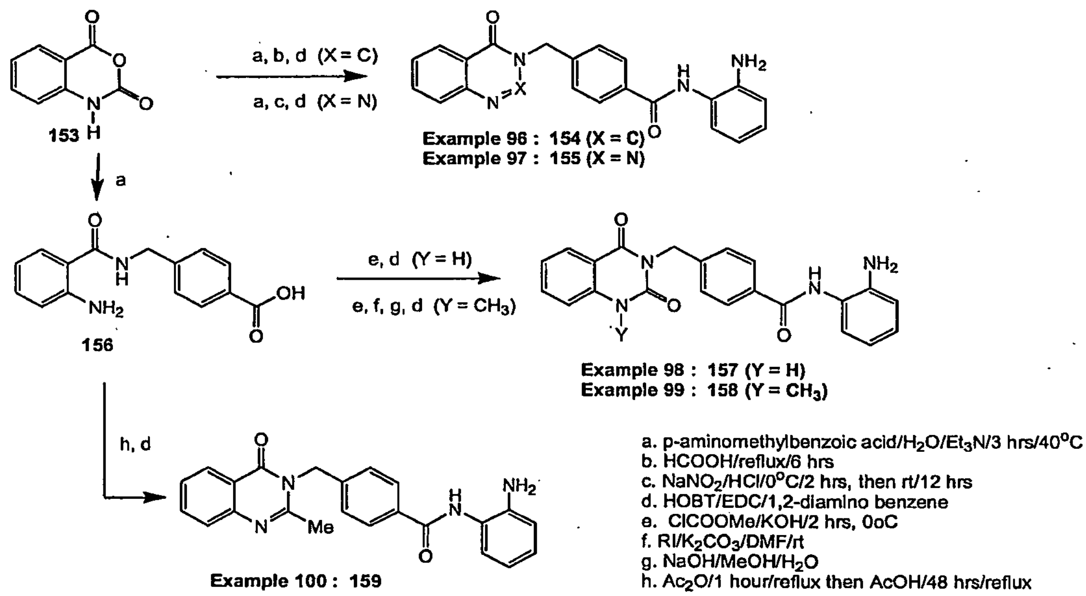
[0235] Following a procedure analogous to that described in Example 94, step 1, but substituting 4-aminomethylbenzoic acid for tyramine the title compound **150** was obtained in 48% yield. LMRS = 268.0 (M+1).

Step 2: 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethyl)-phenyl trifluoromethane-sulfonate (**151**)

[0236] To a solution of sodium hydride (90 mg, 25 mmol) in dry THF (20 mL) at 0°C, **150** (500 mg, 8.9 mmol) was added followed by the addition of dry DMF (2 mL). The reaction mixture was stirred for 20 min at 0°C, treated portionwise with $PhN(Tf)_2$, stirred for additional 2 h and evaporated to produce a solid material which was purified by chromatography on a silica gel column, (CH_2Cl_2 - MeOH (19:1)) to provide **151** (639 mg, 86% yield). LMRS = 400.0 (M+1).

Step 3: *N*-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound **152**)

[0237] Following a procedure analogous to that described in Example 40, step 2, but substituting **151** for **42**, the title compound **152** was obtained in 15% yield. [1]H NMR: (DMSO d_6) □ 9.57 (s, 1H), 7.78-7.87 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 6.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.83 (bs, 2 H), 3.85 (t, J = 7.1 Hz, 2 H), 3.00 (t, J = 7.1 Hz, 2 H).



Example 96

N-(2-Amino-phenyl)-4-(4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 154)

[0238] A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et_3N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride **153** (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and evaporated to form an oily

residue, which was refluxing in formic acid (20 mL) for 7 h. Formic acid was removed in vacuum to produce a solid, which was triturated with water and filtered off to provide the carboxylic acid (1.61 g, 96%). LMRS = 281.0 (M+1).

[0239] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **154** was obtained was obtained in 43% yield. ^{1}H NMR: (DMSO d_6) □ 9.71 (s, 1H), 8.68 (s, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.0, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.4, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.22 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 7.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 5.35 (s, 2 H).

Example 97

***N*-(2-Amino-phenyl)-4-(4-oxo-4*H*-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide (compound 155)**

[0240] A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et_3N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and cooled to 0°C. The cold reaction mixture was acidified with conc. HCl (5 mL) and treated drop wise with $NaNO_2$ solution (520 mg, 7.5 mmol in 5 mL water) over 5 min period of time, then left overnight at room temperature. A precipitate formed which was collected, washed with water and dried to provide the carboxylic acid (1.62 g, 96%). LMRS = 282.0 (M+1).

[0241] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **155** was obtained in 27% yield. ^{1}H NMR: (DMSO d_6) □ 9.62 (s, 1H), 8.25 (t, J = 6.7 Hz, 2H), 8.11 (ddd, J = 7.1 Hz, 1.4 Hz, 1H), 7.93-7.98 (m, 3H), 7.49 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.66 (s, 2 H), 4.87 (bs, 2 H).

Example 98

***N*-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzamide (compound 157)**

Step 1: 4-[(2-Amino-benzoylamino)-methyl]-benzoic acid (compound **156**)

[0242] To a suspension of 4-aminomethylbenzoic acid (5.09 g, 33.7 mmol) in H_2O (50 mL), was added Et_3N (4.7 mL, 33.7 mmol) followed by isatoic anhydride **153** (5.0 g, 30.6 mmol). The brown mixture was heated

at 40°C for 2 h until the mixture became homogeneous and then Et_3N was removed *in vacuo*. The resulting aqueous solution was acidified (10% HCl/H_2O) and the mixture was partitioned between H_2O and ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to give **156** as a white solid (6.0 g, 72 %). LMRS = 271.0 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-ylmethyl)-benzamide (compound 157)

[0243] The carboxylic acid **156** (1.72 g, 6.36 mmol) was suspended in a solution of NaOH (2.55 g, 63.6 mmol) in H_2O (12 mL). To this solution was added dioxane (10 mL) until mixture became homogeneous. The solution was cooled to 0°C in an ice-bath and methyl chloroformate (1.25 mL, 16.1 mmol) was added portionwise over 2 h. After completion of the reaction, the excess methyl chloroformate and dioxane were removed *in vacuo* and the mixture was diluted with methanol (80 mL) and H_2O (20 mL). The solution was heated to 50°C for 1 h. until the cyclization was complete. Methanol was removed in vacuo and then the aqueous layer was extracted with ethyl acetate. Subsequently, the aqueous phase was acidified (10% HCl/H_2O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were combined, dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude was triturated with warm methanol to afford the carboxylic acid as a white solid (1.7 g, 90%). LMRS = 319.0 (M+Na).

[0244] Following a procedure analogous to that described in Example 92, step 2, but substituting the quinazolinedione carboxylic acid for **143**, the title compound **157** was obtained. ^1H NMR: (DMSO-d_6) □ 11.56 (brs, 1H), 9.59 (brs, 1H), 7.96-7.88 (m, 3H), 7.67 (dt, J = 8.4, 1.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92 (dt, J = 6.9, 1.2 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 6.57 (t, J = 6.9 Hz, 1H), 5.15 (brs, 2H), 4.86 (brs, 2H).

Example 99

N-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 158)

Step 2: 4-(1-Methyl-2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-ylmethyl)-benzoic acid methyl ester

[0245] To a solution of the quinazolinedione carboxylic acid (1.0 g, 3.38 mmol) in DMF (7 mL), was added K_2CO_3 (1.4 g, 10.1 mmol) and the mixture was then cooled to 0°C. Subsequently, MeI (1.05 mL, 16.9

mmol) was added and the mixture was allowed to warm to rt in the ice bath overnight. Excess methyl iodide and DMF were removed *in vacuo* and the crude was partitioned between ethyl acetate and H_2O. The aqueous phase was washed again with ethyl acetate, the combined organic extracts were dried over Na_2SO_4 and then concentrated *in vacuo* to yield the desired product as an off-white solid (0.93 g, 85%). LMRS = 325.0 (M+1).

Step 3: 4-(1-Methyl-2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-ylmethyl)-benzoic acid

[0246] To a suspension of the methyl ester (1.25 g, 3.85 mmol) in methanol (35 mL), was added 1N NaOH (30 mL, 38.5 mmol) and the mixture was heated to 45-50°C for 3 h. until it became homogeneous. Methanol was removed *in vacuo* and the crude was partitioned between ethyl acetate and H_2O. The aqueous phase was acidified (10% HCl/H2O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford product 5 as a white solid (1.15 g, 96%). LMRS = 311.0 (M+1).

Step 4: *N*-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-ylmethyl)-benzamide (compound **158**)

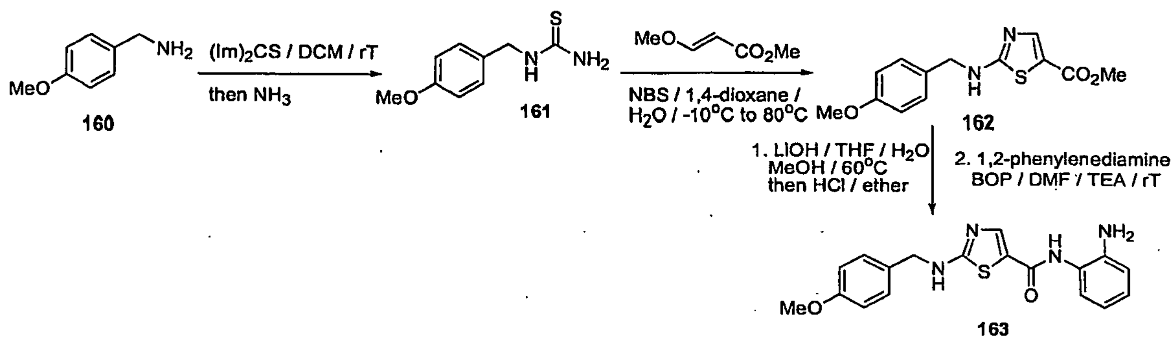
[0247] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **158** was obtained in 10% yield. ^{1}H NMR: (DMSO-d_6) δ 9.59 (brs, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 2H) 7.80 (dt, J = 6.9, 1.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 5.21 (brs, 2H), 4.86 (brs, 2H), 3.54 (s, 3H).

Example 100

N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 159)

[0248] A suspension of **156** (903 mg, 3.34 mmol) in acetic anhydride (15 mL) was heated at 50°C for 1 h. Acetic anhydride was evaporated under vacuum and the solid material formed was dissolved in acetic acid (30 mL). This solution was refluxed 48h and evaporated to form another solid material, which was recrystallized from a mixture AcOEt/$CHCl_3$ to produce the intermediate carboxylic acid (420 mg, 43% yield). LMRS = 385.0 (M+1).

[0249] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for **143**, the title compound **159** was obtained in 49 % yield. ^{1}H NMR: (DMSO) δ (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H, overlaps with the DMSO signals).



Example 101

Example 101

N-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound 163)

Step 1: 4-Methoxybenzyl-thiourea (compound **161**)

[0250] To a solution of thiocarbonyl diimidazole (1.23g, 6.22 mmol, 1.5 equiv.) in dry dichloromethane (10 mL), neat alkylamine **160** (4.15 mmol, 1.0 equiv.) was added dropwise at 0°C, and the solution stirred from 0°C to 15°C during 16 h. A solution of concentrated ammonium hydroxide (3 mL, 45 mmol, 3.6 equiv.) in 1,4-dioxane (6 mL) was added at 0°C and stirred at room temperature for 7 h. The solution was diluted with ethyl acetate (250 mL), washed with brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated. After purification by column chromatography (silica gel, elution 5% methanol in dichloromethane), **161** was obtained as yellow solid (700.2 mg, 3.6 mmol, 86% yield). ^{1}H NMR: (Acetone-d_6) δ (ppm): 7.53 (bs, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.67 (bs, 2H), 4.67 (s, 2H), 3.77 (s, 3H). LMRS = 197.1 (M+1).

Step 2: 2-(4-Methoxybenzylamino)thiazole-5-carboxylic acid methyl ester (compound **162**)

[0251] A solution of trans methyl-2-methoxyacrylate (461 mg, 3.97 mmol, 1 equiv.) in 50% 1,4-dioxane in water (4 mL) stirred at –10°C, was treated with *N*-bromosuccinimide (792 mg, 4.46 mmol, 1.12 equiv.), stirred at the same temperature for 1h, transferred to a flask containing the thiourea **161** (700.2 mg, 3.6 mmol) and the mixture was stirred at 80°C for 2h. After cooling down to room temperature, concentrated NH_4OH (0.8 mL) was added, stirred for 10 min and the resulting precipitated filtered and washed with water, giving 363 mg (1.3 mmol, 36% yield) of **162**, plus 454 mg additional (91 % pure by HPLC) as residue from evaporation of the filtrated (ca. 77% overall yield). ^{1}H NMR: (Acetone-d_6) δ (ppm): 7.97 (bs, 1H), 7.72 (bs, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H). LMRS = 279.1 (M+1).

Step 3: *N*-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound **163**)

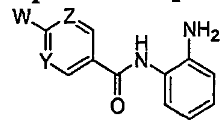
[0252] Following the procedure described in Example 1, steps 4 and 5, but substituting **162** for **6**, the title compound **163** was obtained in 50% yield. ^{1}H-NMR (methanol-*d4*), δ (ppm): 7.86 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.11 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.04 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.86 (m, 1H), 6.74 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.85 (bs, 4H), 4.45 (s, 2H), 3.78 (s, 3H).

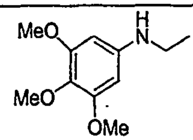
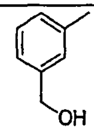
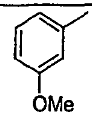
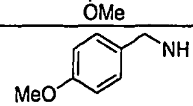
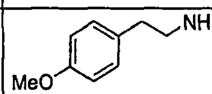
Examples 102-121

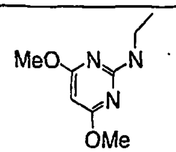
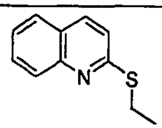
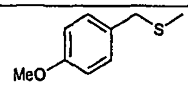
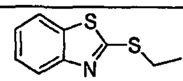
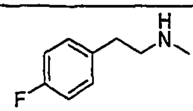
[0253] Examples 102 to 121 describe the preparation of compounds **164** to **183** using the same procedures as described for compounds **62** to **163** in Examples 47 to 101. Characterization data are presented in Tables 4a and 4b.

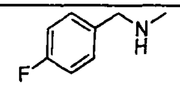
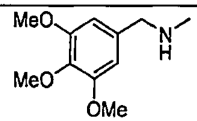
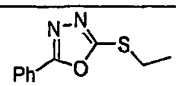
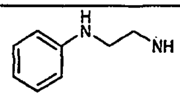
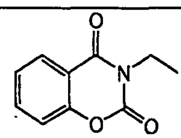
Table 4a

Characterization of Compounds Prepared in Examples 102-121



Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
102	164		CH	CH	*N*-(2-Amino-phenyl)-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-benzamide	^{1}H NMR: (Acetone-d_6) δ (ppm): 9.09 (bs, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.00 (t, J = 6.6 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.67 (t, J= 8.0 Hz, 1H), 5.99 (s, 2H), 5.46 (bs, 1H), 4.64 (bs, 2H), 4.43 (s, 2H), 3.69 (s, 6H), 3.60 (s, 3H).	11
103	165		N	CH	*N*-(2-Amino-phenyl)-6-(3-hydoxymethyl-phenyl)-nicotinamide	^{1}H NMR (20% CD_3OD in $CDCl_3$) δ (ppm): 9.14 (d, J = 1.8 Hz, 1H), 8.33 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.93 (s, 1H), 7.82 (m, 2H), 7.50-7.40 (m, 2H), 7.22-6.45 (m, 4H), 4.69 (s, 2H).	15
104	166		CH	CH	*N*-(2-Amino-phenyl)-4-(3-methoxy-phenyl)-benzamide	^{1}H NMR (CD_3OD) δ (ppm): 7.98 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.31-7.04 (m, 5H), 6.92-6.80 (m, 3H), 3.84 (s, 3H).	15
105	167		CH	N	*N*-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide	^{1}H NMR (DMSO-d_6) δ (ppm): 9.33 (s, 1H), 8.61 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 5.8 Hz, 1H), 7.24 (d, J = 8.52 Hz, 2 H), 7.11 (d, J = 7.69 Hz, 1H), 6.90 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.50-6.58 (m, 2H), 4.83 (s, 2H), 4.45 (d, J = 5.8 Hz, 2H), 3.70 (s, 3H).	6
106	168		CH	N	*N*-(2-amino-phenyl)-6-[2-(4-methoxy-phenyl)-ethylamino]-nicotinamide	^{1}H NMR (DMSO-d_6) δ (ppm): 9.42 (s, 1H), 8.72 (d, J = 2.5 Hz, 1H), 7.97 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 7.23 (m, 4H), 6.81-7.03 (m, 4H), 6.64 (m, 1H), 6.56 (d, J = 9.1 Hz, 1H), 4.92 (s, 2H), 3.78 (s, 3H), 3.55 (m, 2H), 2.85 (t, J = 7.3 Hz, 2H).	6

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
107	169		CH	CH	*N*-(2-Amino-phenyl)-4-[(4,6-dimethoxy-pyrimidin-2-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d$_6$)** δ (ppm): 9.63 (bs, 1H), 7.95 (d, J = 7.9 Hz, 2H), 7.85-7.82 (m, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.03 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.9 Hz, 7.7 Hz, 1H), 4.94 (bs, 2H), 4.54 (d, J = 6.0 Hz, 2H), 3.79 (bs, 6H).	11
108	170		CH	CH	*N*-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide	**^{1}H NMR: (DMSO-d$_6$)** δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).	11
109	171		N	CH	*N*-(2-Amino-phenyl)-6-(4-methoxy-benzylsulfanyl)-nicotinamide	**^{1}H NMR: (DMSO-d$_6$)** δ (ppm): 9.06 (bs, 1H), 8.17 (dt, J = 10.9 Hz, 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.21-7.13 (m, 2H), 7.01 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 5.01 (bs, 2H), 4.47 (s, 2H), 3.76 (s, 3H).	12
110	172		CH	CH	*N*-(2-Amino-phenyl)-4-(benzothiazol-2-ylsulfanylmethyl]-benzamide	**^{1}H NMR: (DMSO-d$_6$)** δ (ppm): 8.01 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.90 (dd, J = 4.4 Hz, 0.6 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.48 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 7.37 (td, J = 7.1 Hz, 1.1 Hz, 1H), 7.14 (d, J = 7.1 Hz, 1H), 6.96 (t, J = 6.3 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.58 (t, J = 6.6 Hz, 1H), 4.88 (s, 2H), 4.73 (s, 2H).	11
112	174		CH	N	*N*-(2-amino-phenyl)-6-[2-(4-fluoro-phenyl)-ethylamino]-nicotinamide	**^{1}H NMR (DMSO-d$_6$)** δ (ppm): 9.34 (s, 1H), 8.64 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 9 Hz, 2 Hz, 1H), 7.16-7.22 (m, 3H), 7.06-7.20 (m, 3H), 6.90-6.96 (m, 1H), 6.72-6.78 (m, 1H), 6.46-6.60 (m, 2H), 4.92 (s, 2H), 3.50 (m, 2H), 2.92 (m, 2H).	6

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
113	175		CH	N	*N*-(2-amino-phenyl)-6-(4-fluoro-benzylamino)-nicotinamide	^{1}**H NMR (DMSO-d$_6$)** δ (ppm): 9.34 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 7.91 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.66 (t, J = 6 Hz, 1H), 7.32-7.37 (m, 2H), 7.08 –7.38 (m, 3H), 6.93 (m, 1H), 6.74 (m, 1H), 6.52-6.58 (m, 2H), 4.84 (s, 2H), 4.51 (d, J = 6.0 Hz)	6
114	176		CH	N	*N*-(2-amino-phenyl)-6-(3,4,5-trimethoxy-benzylamino)-nicotinamide	^{1}**H NMR (DMSO-d$_6$)** δ (ppm): 9.34 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 6 Hz, 1H), 7.10 (m, 1H), 6.93 (m, 1H), 6.74 (m, 1H), 6.66 (s, 2H), 6.56 (m, 2H), 4.84 (s, 2H), 4.45 (d, J = 6 Hz, 2H), 3.73 (s, 6H), 3.31 (s, 3H).	6
115	177		CH	CH	*N*-(2-Amino-phenyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanylmethyl]-benzamide	^{1}**H NMR: (Acetone-d$_6$)** δ (ppm): 9.08 (bs, 1H), 8.02 (dd, J = 7.1 Hz, 1.9 Hz, 4H), 7.69 (d, J = 8.5 Hz, 2H), 7.62-7.57 (m, 3H), 7.28 (d, J = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, J = 6.6 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 4.70 (s, 2H), 4.63 (bs, 2H).	14
116	178		N	CH	*N*-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide	^{1}H-NMR (CD_3OD-*d4*), δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J= 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt, J= 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H).	11
117	179		CH	CH	*N*-(2-Amino-phenyl)-4-(2,4-dioxo-4*H*-benzo[e][1,3]oxazin-3-ylmethyl)-benzamide	^{1}**H NMR: (DMSO-d$_6$)** δ (ppm): 9.62 (s, 1H), 8.00 (dd, J = 8.2 Hz, 1.9 Hz, 1H), 7.80-7.92 (m, 3H), 7.42-7.50 (m, 4H), 7.13 (d, J = 7.1 Hz, 1H), 6.95 (ddd, J = 8.0 Hz, 1.6 Hz, 1H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.13 (s, 2H), 4.87 (bs, 2H).	11

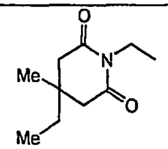
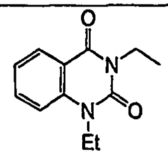
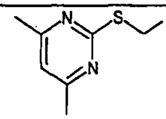
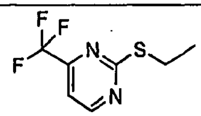
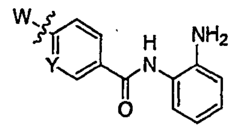
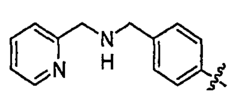
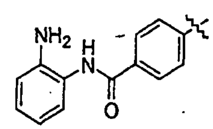
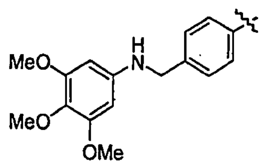
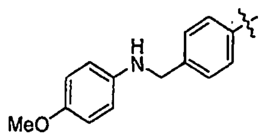
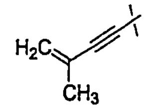
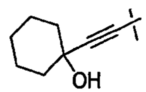
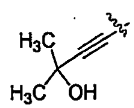
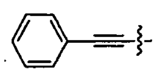
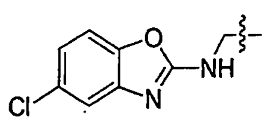
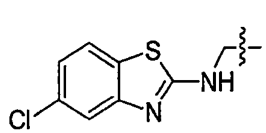
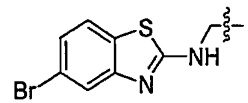
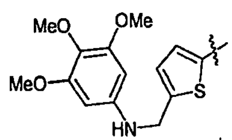
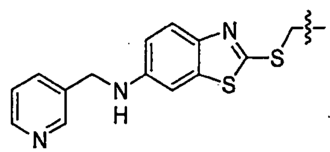
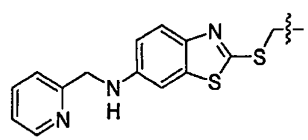
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
118	180		CH	CH	*N*-(2-Amino-phenyl)-4-(4-ethyl-4-methyl-2,6-dioxo-piperidin-1-ylmethyl)-benzamide	^{1}**H NMR: (DMSO-d$_6$)** δ (ppm): 9.59 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.86 (bs, 2H), 2.61 (s, 2H), 2.55 (s, 2H), 1.31 (q, J = 7.7 Hz, 2H), 0.91 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H).	11
119	181		CH	CH	*N*-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzamide	^{1}**H NMR: (CDCl$_3$)** δ (ppm): 8.23 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 8.01 (bs, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.71-7.65 (m, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (dt, J = 7.7, 1.5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3 Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H).	19
120	182		CH	CH	*N*-(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide	^{1}**H NMR: (DMSO-d$_6$)** δ (ppm): 9.66 (bs, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H).	11
121	183		CH	CH	*N*-(2-Amino-phenyl)-4-(4-trifluoromethyl-pyrimidin-2-ylsulfanylmethyl)benzamide	^{1}**H NMR: (DMSO-d$_6$)** δ (ppm): 9.66 (bs, 1H), 9.07 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.78 (d, J = 4.7 Hz, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.64 (dt, J = 7.4 Hz, 7.1 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H).	11

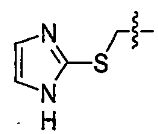
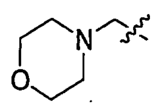
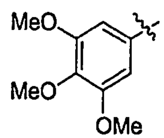
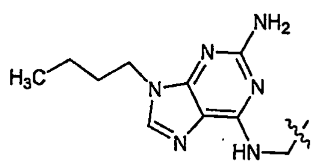
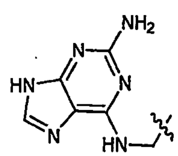
Table 4b

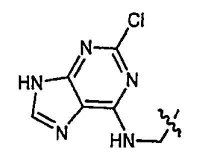
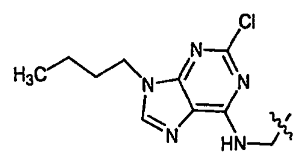
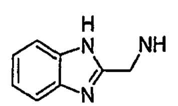
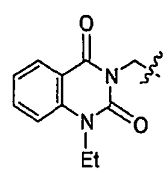
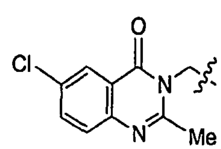


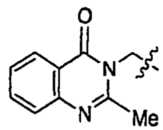
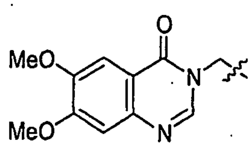
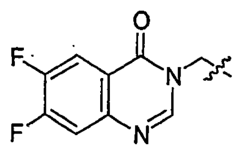
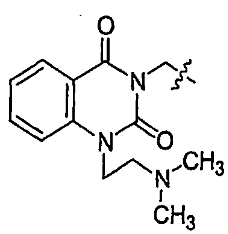
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
123	187		CH	CH	*N*-(2-Aminophenyl)-4-[3-(pyridin-2ylmethyl-aminomethyl)phenyl)]-benzamide	**^{1}H NMR (20% CD_3OD in $CDCl_3$)** δ (ppm): 8.46 (m, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.64-6.70 (m, 14 H), 3.80 (br s, 4H).	21
124	188		CH	CH	Biphenyl-4,4'-dicarboxylic acid bis-[(2-amino-phenyl)-amide]	**^{1}H NMR (CD_3OD)** δ (ppm): 9.80 (bs, 2H), 8.16 (d, J=7.9 Hz, 4H), 7.96 (d, J= 7.9 Hz, 4H), 7.23 (d, J=7.4 Hz, 2H), 7.03 (dd, J=6.9, 7.4 Hz, 2H), 6.84 (d, J=8.2 Hz, 2H), 6.66 (dd, J=6.9, 7.7 Hz, 2H), 5.06 (bs, 4H).	1
125	189		CH	CH	*N*-(2-Amino-phenyl)-4-[4-{(3,4,5-trimethoxy-phenylamino)-methyl}-phenyl]-benzamide	**^{1}H NMR (DMSO-d_6)** δ (ppm): 10.15 (1H, brs), 8.17 (2H, d, J=8.0), 7.90 (2H, d, J=8.2), 7.87 (1H, brs), 7.72 (1H, d, J=6.6), 7.54 (2H, m), 7.40 (1H, d, J=8.5), 7.25 (1H, m), 7.16 (1H, d, J=7.4), 7.07 (1H, m), 6.08 (2H, s), 4.42 (2H, s), 3.73 (6H, s), 3.58 (3H, d, J=0.8)	21
126	190		CH	CH	*N*-(2-Amino-phenyl)-4-[4-{(4-methoxy-phenylamino)-methyl}-phenyl]-benzamide	**^{1}H NMR (DMSO-d_6)** δ (ppm): 10.03 (1H, brs), 8.17 (2H, d, J=7.7), 7.88 (3H, m), 7.76 (1H, d, J=7.1), 7.52 (2H, m), 7.35 (1H, d, J=8.0), 7. 17 (1H, m), 7.08-6.93 (6H, m), 4.50 (3H, s), 3.75 (2H, s)	21

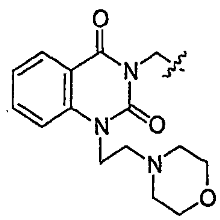
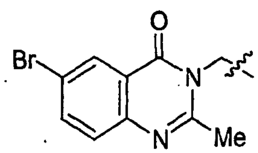
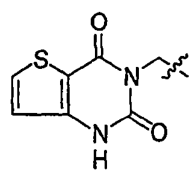
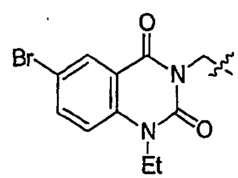
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
128	193		CH	CH	*N*-(2-Amino-phenyl)-4-(3-methyl-but-3-en-1-ynyl)-benzamide	LRMS calc: 276.03, found: 277.2 $(MH)^+$	22
129	194		CH	CH	*N*-(2-Amino-phenyl)-4-(1-hydroxy-cyclohexylethynyl)-benzamide	LRMS calc: 334.4, found: 335 $(MH)^+$	22
130	195		CH	CH	*N*-(2-Amino-phenyl)-4-(3-hydroxy-3-methyl-but-1-ynyl)-benzamide	LRMS calc: 294.35, found: 295.1 $(MH)^+$	22
131	196		CH	CH	*N*-(2-Amino-phenyl)-4-phenylethynyl-benzamide	LRMS calc: 312.37, found: 313.2 $(MH)^+$	22
180	320		CH	CH	*N*-(2-Amino-phenyl)-4-[(5-chloro-benzooxazol-2-ylamino)-methyl]-benzamide	**^{1}H NMR: (Acetone-d_6)** δ (ppm): 9.67 (s, 1H), 8.85 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.8, 2.3 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.65 (t, 7.0 Hz, 1H), 4.94 (s, 2H), 4.67 (d, J = 5.3 Hz, 2H).	35
181	321		CH	CH	*N*-(2-Amino-phenyl)-4-{[4-(4-chloro-phenyl)-thiazol-2-ylamino]-methyl}-benzamide	**^{1}H NMR: (DMSO-d_6)** δ (ppm): 9.67 (bs, 1H), 8.36 (t, J = 5.8 Hz, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.20 (s, 1H), 7.02 (**t**, J = 8.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.65 (t, J = 7.1 Hz, 1H), 4.92 (bs, 2H), 4.65 (d, J = 5.8 Hz, 2H).	35

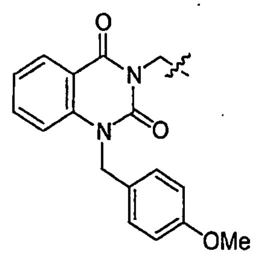
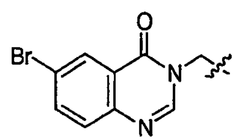
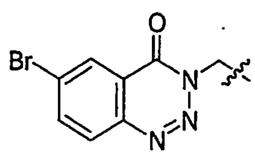
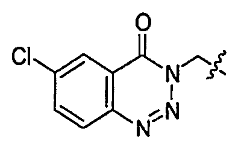
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
182	322		CH	CH	*N*-(2-Amino-phenyl)-4-[(5-bromo-benzothiazol-2-ylamino)-methyl]-benzamide	[1]H NMR: (DMSO-d_6) δ (ppm): 6.97 (s, 1H), 8.78 (bs, 1H), 8.01 (d, J = 8.8 Hz, 2H), 8.00 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.43-7.35 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 4.94 (s, 2H), 7.74 (d, J=5.9 Hz, 2H).	33, 34
183	323		CH	CH	*N*-(2-Amino-phenyl)-4-{5-[(3,4,5-trimethoxy-phenylamino)-methyl]-thiophen-2-ylmethyl}-benzamide	LRMS calc: 489.58, found: 490 $(MH)^+$	21
184	325		CH	CH	*N*-(2-Amino-phenyl)-4-{6-[(pyridin-3-ylmethyl)-amino]-benzothiazol-2-ylsulfanylmethyl}-benzamide	[1]H NMR: (Acetone-d_6) δ (ppm): 8.65 (d, J = 1.4 Hz, 1H), 8.44 (dd, J = 4.7, 3.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.81-7.77 (m, 1H), 7.63 (m, 3H), 7.33-7.26 (m, 2H), 7.09 (d, J=2.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 6.86 (dd, J = 8.0, 1.4 Hz, 1H), 6.69-6.64 (m, 1H), 4.64 (s, 2H), 4.47 (s, 2H).	11
185	326		CH	CH	*N*-(2-Amino-phenyl)-4-{6-[(pyridin-2-ylmethyl)-amino]-benzothiazol-2-ylsulfanylmethyl}-benzamide	[1]H NMR: (DMSO-d_6) δ (ppm): 9.59 (s, 1H), 8.52-8.51 (m, 1H), 7.89 (d, J= 8.24 Hz, 2H), 7.71 (td, J = 7.7,1.9 Hz, 1H), 7.59-7.53 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.12 (d, J = 6.9, Hz, 1H), 6.98-6.96 (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.81 (dd, J = 9.1, 2.5 Hz, 1H), 6.76-6.73 (m, 1H), 6.67 (t, J = 5.8 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.87 (s, 1H), 4.58 (s, 2H), 4.38 (d, J = 6.3 Hz, 2H).	11, 34

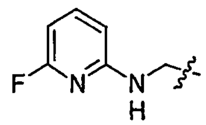
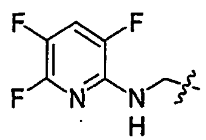
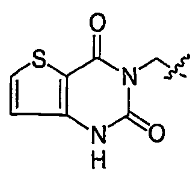
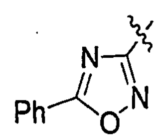
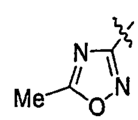
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
186	327		CH	CH	*N*-(2-Amino-phenyl)-4-(1H-imidazol-2-ylsulfanylmethyl)-benzamide	^{1}**H NMR: (DMSO-d$_6$)** δ (ppm): 12.23 (bs, 1H), 9.59 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.14-7.12 (m, 2H), 6.94-6.92 (m, 2H), 6.76 (d, J = 6.6 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.29 (s, 2H).	14
187	328		CH	CH	*N*-(2-Amino-phenyl)-4-morpholin-4-ylmethyl-benzamide	^{1}**H NMR: (CD$_3$OD)** δ (ppm): 8.03 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 7.0 Hz, 1H), 7.16 (t, J = 6.6 Hz, 1H), 6.98 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 3.78 (t, J = 4.4 Hz, 4H), 3.68 (s, 2H), 2.57-2.54 (m, 4H).	37
188	329		CH	CH	3',4',5'-Trimethoxy-biphenyl-4-carboxylic acid (2-amino-phenyl)-amide	^{1}**H NMR: (CD$_3$OD)** δ (ppm): 8.14 (d, J = 7.9 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.17 (t, J = 7.0 Hz, 1H), 7.04 (s, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 7.5Hz, 1H), 4.95 (s, 6H), 4.01 (s, 3H).	37
189	330		CH	CH	4-[(2-Amino-9-butyl-*9H*-purin-6-ylamino)-methyl]-*N*-(2-amino-phenyl)-benzamide	^{1}**H NMR: (DMSO-d$_6$)** δ (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.7 Hz, 2H), 7.95 (bs, 2H) 7.78 (s, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (dd, J = 7.3, 8.0 Hz, 1H), 6.8 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 7.3, 7.7 Hz, 1H), 5.91 (s, 2H), 4.94 (bs, 2H), 4.77 (bs, 2H), 4.01 (t, J = 7.1 Hz, 1H), 1.78 (m, 2H), 1.3 (m, 2H), 0.95 (t, J =7.4, Hz, 1H)	39
190	331		CH	CH	*N*-(2-Amino-phenyl)-4-[(2-amino-*9H*-purin-6-ylamino)-methyl]-benzamide	^{1}**H NMR (DMSO-d$_6$)** δ (ppm): 10.16 (s, 1H), 9.60 (br, 1H), 8.24 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.62 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.20 (m, 2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H)	39

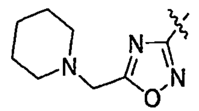
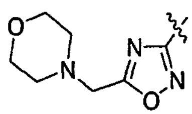
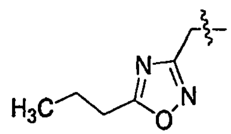
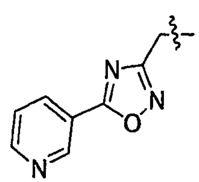
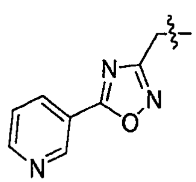
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
191	332		CH	CH	*N*-(2-Amino-phenyl)-4-[(2-chloro-9*H*-purin-6-ylamino)-methyl]-benzamide	**^{1}H NMR (DMSO-d$_6$)** δ (ppm): 9.67 (m, 1H), 8.80 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7,02 (dd, J = 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (d6, J = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H)	39
192	333		CH	CH	*N*-(2-Amino-phenyl)-4-[(9-butyl-2-chloro-9*H*-purin-6-ylamino)-methyl]-benzamide	**^{1}H NMR (DMSO-d$_6$)** δ (ppm): 9.60 (s, 1H), 8.72 (br, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 6.7, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (dd, J = 6.7, 8.0 Hz, 2H), 4.88 (s, 1H), 4.71 (m, 2H), 4.11 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 0.89 (t, J=7.1 Hz, 3H)	39
193	334		CH	CH	*N*-(2-Amino-phenyl)-4-[(1H-benzoimidazol-2-ylmethyl)-amino]-benzamide	**^{1}H NMR: (DMSO-d$_6$)** δ (ppm): 12.39 (bs, 1H), 9.32 (s, 1H), 7.81 (d, J=8.2 Hz, 2H), 7.56 (bs, 1H), 7.21-7.17 (m, 3H), 6.99-6.97 (m, 2H), 6.81 (d, J=8.2 Hz, 1H), 6.77 (d, J=8.8 Hz, 2H), 6.63 (t, J=7.0 Hz, 1H), 4.85 (s, 2H), 4.62 (d, J=5.3 Hz, 2H).	11
194	335		CH	CH	*N*-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzamide	**^{1}H NMR: (CDCl$_3$)** δ (ppm): 8.23 (dd, J = 7.8, 1.5 Hz, 1H), 8.01 (bs, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.71-7.65 (m, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (td, J = 7.7, 1.5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3 Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H). **MS:** (calc.) 414.2; (obt.) 415.3 $(MH)^+$	19
195	336		CH	CH	N-(2-Amino-phenyl)-4-(6-chloro-2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.69 (bs, 1H, N*H*), 8.71 (s, 1H), 8.16 (d, J = 2.5 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.02 (td, J = 7.6, 1.5 Hz, 1H), 6.82 (dd, J = 8.0, 1.4 Hz, 1H), 6.64 (td, J = 7.6, 1.4 Hz, 1H), 5.34 (s, 2H), 4.94 (bs, 2H). **MS:** (calc.) 404.1; (obt.) 405.0 $(MH)^+$	19

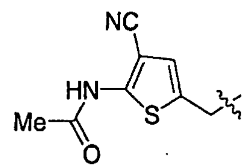
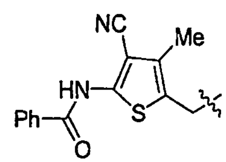
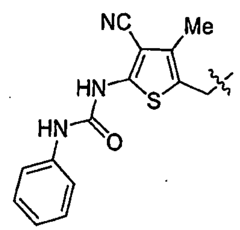
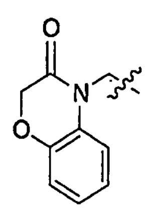
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
196	337		CH	CH	N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H). **MS**: (calc.) 384.2; (obt.) 385.0 $(MH)^+$	19
197	338		CH	CH	N-(2-Amino-phenyl)-4-(6,7-dimethoxy-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.62 (bs, 1H), 8.50 (s, 1H), 8.41 (d, J = 8.2 Hz, 2H), 7.47 (s, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.17 (s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.96 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.58 (dd, J = 6.9, 6.9 Hz, 1H), 5.26 (s, 2H), 4.88 (bs, 2H), 3.91 (s, 3H), 3.87 (s, 3H). **MS**: (calc.) 430.2; (obt.) 431.1 $(MH)^+$	19
198	339		CH	CH	N-(2-Amino-phenyl)-4-(6,7-difluoro-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.66 (bs, 1H), 8.69 (s, 1H), 8.07 (dd, J = 8.8, 10.4 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 14.3, 11.3 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.76 (dd, J = 8.1, 1.2 Hz, 1), 6.58 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.28 (s, 2H), 4.89 (bs, 2H). **MS**: (calc.) 406.1; (obt.) 407.0 $(MH)^+$	19
199	340		CH	CH	N-(2-Amino-phenyl)-4-[1-(2-dimethylamino-ethyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 7.8, 1.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.81 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.14 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 7.8, 1.2 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.22 (s, 2H), 4.88 (bs, 2H), 4.24 (t, J = 7.1 Hz, 2H), 2.5 (m, 2H) 2.22 (s, 6H). **MS**: (calc.) 457.2; (obt.) 458.1 $(MH)^+$	19

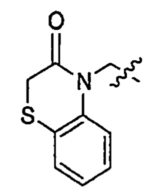
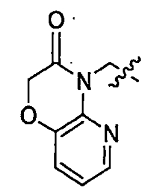
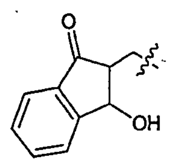
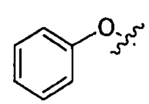
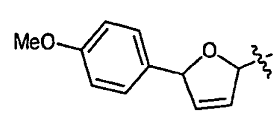
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
200	341		CH	CH	N-(2-Amino-phenyl)-4-[1-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide	^{1}**H NMR: (DMSO)** δ (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 8.0, 1.6 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.81 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.4, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.22 (s, 2H), 4.87 (bs, 2H), 4.28 (t, J = 6.7 Hz, 2H), 3.50 (t, J = 4.5 Hz, 4H), 2.58 (t, J = 6.7 Hz, 2H), 2.47-2.44 (m, 4H). **MS**: (calc.) 499.2; (obt.) 500.3 $(MH)^+$.	19
201	342		CH	CH	N-(2-Amino-phenyl)-4-(6-bromo-2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide	^{1}**H NMR: (DMSO)** δ (ppm): 9.65 (bs, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.99 (ddd, J = 8.5, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.45 (s, 2H), 4.88 (bs, 2H). **MS**: (calc.) 462.1; (obt.) 463.1 $(MH)^+$.	19
202	343		CH	CH	N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide	^{1}**H NMR: (DMSO)** δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 5.2, 0.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 5.12 (s, 2H), 4.88 (bs, 2H). **MS**: (calc.) 392.1; (obt.) 393.0 $(MH)^+$.	43
203	344		CH	CH	N-(2-Amino-phenyl)-4-(6-bromo-1-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide	^{1}**H NMR: (DMSO)** δ (ppm): 9.61 (bs, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 9.1, 4.9 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 9.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.20 (s, 2H), 4.88 (bs, 2H) 4.14 (q, J = 7.0, 2H), 1.21 (t, J = 7.0, 3H). **MS**: (calc.) 492.1; (obt.) 493.0 $(MH)^+$.	19

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
204	345		CH	CH	N-(2-Amino-phenyl)-4-[1-(4-methoxy-benzyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.62 (bs, 1H), 8.10 (dd, J = 7.7, 1.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.71 (ddd, J = 7.9, 7.9, 1.5 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 6.6 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.33 (s, 2H), 5.28 (s, 2H), 4.89 (bs, 2H), 3.71 (s, 3H). **MS**: (calc.) 506.2; (obt.) 507.1 $(MH)^+$.	19
205	346		CH	CH	N-(2-Amino-phenyl)-4-(6-bromo-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.61 (bs, 1H), 8.66 (s, 1H), 8.24 (d, J = 2.5 Hz, 1H), 8.00 (dd, J = 8.7, 2.3 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.28 (s, 2H), 4.87 (bs, 2H). **MS**: (calc.) 448.0; (obt.) 449.0 $(MH)^+$.	19
206	347		CH	CH	N-(2-Amino-phenyl)-4-(6-bromo-4-oxo-4H-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.63 (bs, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.28 (dd, J = 8.8, 2.2 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 7.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.67 (s, 2H), 4.87 (bs, 2H). **MS**: (calc.) 449.0; (obt.) 450.0 $(MH)^+$.	19
207	348		CH	CH	*N*-(2-Amino-phenyl)-4-(6-chloro-4-oxo-4H-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.63 (bs, 1H), 8.30-8.24 (m, 2H), 8.15 (ddd, J = 8.6, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H*H*), 7.15 (d, J = 8.0 Hz, 1H), 7.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.67 (s, 2H), 4.88 (bs, 2H). **MS**: (calc.) 405.1; (obt.) 406.0 $(MH)^+$.	19

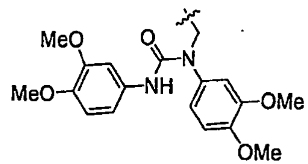
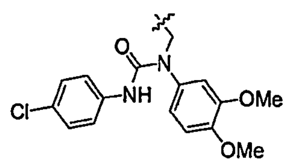
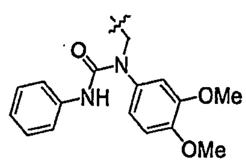
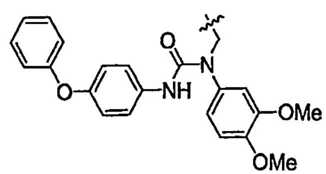
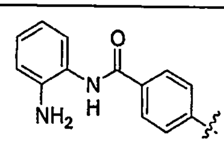
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
208	349		CH	CH	*N*-(2-Amino-phenyl)-4-[(3-fluoro-2-pyridinyl-amino)-methyl]-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.07 (bs, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.64-7.44 (m, 3H), 7.33 (dd, J = 7.8, 1.5 Hz, 1H), 7.03 (td, J =7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.78 (bs, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.48 (dd, J = 8.1, 2.6 Hz, 1H), 6.16 (dd, J = 7.7, 2.5 Hz, 1H), 4.76-4.55 (m, 4H). HRMS (calc.): 336.1386, (found): 336.1389.	11
209	350		CH	CH	*N*-(2-Amino-phenyl)-4-[(3,4,5-trifluoro-2-pyridinyl-amino)-methyl]-benzamide	**^{1}H NMR (acetone-d_6)** δ (ppm): 9.06 (bs, 1H), AB system (δ_A = 8.02, δ_B = 7.56, J = 8.3 Hz, 4H), 7.74-7.65 (m, 1H), 7.33 (d, J = 8.0, 1H), 7.03 (td, J =7.6, 1.5 Hz, 1H), 6.96-6.83 (m, 2H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 4.74 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H).	11
210	351		CH	CH	N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 5.2, 0.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 5.12 (s, 2H), 4.88 (bs, 2H). **MS**: (calc.) 392.1; (obt.) 393.0 $(MH)^+$.	43
211	352		CH	CH	N-(2-Amino-phenyl)-4-(5-phenyl-[1,2,4]oxadiazol-3-yl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.85 (bs, 1H), 8.24-8.19 (m, 6H), 7.79-7.66 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.00 (dd, J = 7.3, 7.3 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.3, 7.3 Hz, 1H), 4.96 (bs, 2H). **MS**: (calc.) 356.1; (obt.) 357.0 $(MH)^+$.	50
212	353		CH	CH	N-(2-Amino-phenyl)-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.81 (bs, 1H), 8.17-8.11 (m, 4H), 7.18 (d, J = 7.9 Hz, 1H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (bs, 2H), 2.70 (s, 3H). **MS**: (calc.) 294.1; (obt.) 295.0 $(MH)^+$.	50

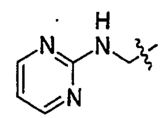
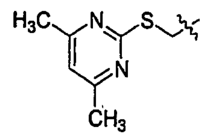
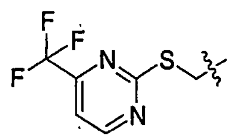
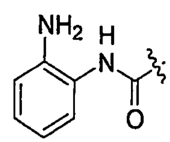
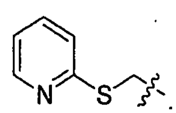
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
213	354		CH	CH	N-(2-Amino-phenyl)-4-(5-piperidin-1-ylmethyl-[1,2,4]oxadiazol-3-yl)-benzamide	**1H NMR: (acetone)** δ (ppm): 9.29 (bs, 1H), 8.21 (m, 4H), 7.31(d, J = 8.0Hz, 1H), 7.03(dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.68 (bs, 2H), 3.94 (s, 2H), 2.58 (t, J= 5.1 Hz), 1.63-1.55 (m, 4H), 1.47-1.43 (m, 2H). **MS** (Calc) 377.2; (Obt.) 378.3(MH)+	50
214	355		CH	CH	N-(2-Amino-phenyl)-4-(5-morpholin-4-ylmethyl-[1,2,4]oxadiazol-3-yl)-benzamide	**1H NMR: (acetone)** δ (ppm): 9.28 (bs, 1H), 8.21 (m, 4H), 7.31(d, J = 8.1 Hz, 1H), 7.03 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.67 (bs, 2H), 4.01 (s, 2H), 3.66 (t, J= 4.8Hz), 2.65 (t, J= 4.4 Hz). **MS:** (Calc.) 379.2; (Obt.): 380.2 (MH)+	50
215	356		CH	CH	N-(2-Amino-phenyl)-4-(5-propyl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.62 (s, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.88 (s, 2H), 4.16 (s, 2H), 2.87 (t, 7.0, 2H), 1.72 (q, J = 7.5 Hz, 2H), 0.92 (t, J = 7.0 Hz, 3H). $(MH)^+$: 337.2.	50
216	357		CH	CH	N-(2-Amino-phenyl)-4-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.64 (s, 1H), 9.24 d, J = 1.8 Hz, 1H); 8.86 (dd, J = 1.3 Hz, J = 4.8 Hz, 1H), 8.45 (dd, J = 1.8 Hz, J = 6.2 Hz, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.66 (dd, J = 4.8 Hz, J = 7.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.89 (s, 2H), 4.31 (s, 2H). $(MH)^+$.372.3.	50
217	358		CH	CH	N-(2-Amino-phenyl)-4-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.63 (s, 1H), 8.87 (d, J = 6.2 Hz, 2H); 7.95-8.02 (m, 3H), 7.50 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.33 (s, 2H). $(MH)^+$: 372.3.	50

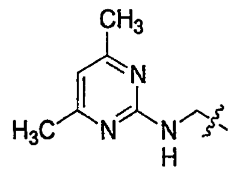
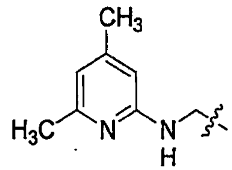
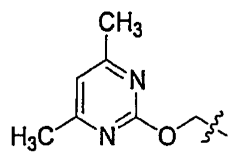
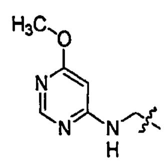
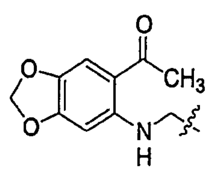
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
218	359		CH	CH	4-(5-Acetylamino-4-cyano-thiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide	**1H NMR (DMSO)** δ (ppm): 11.62 (s, 1H), 9.60 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 6.591 (dd, J = 7.7, 7.7 Hz, 1H), 4.89 (bs, 2H), 4.13 (s, 2H), 2.17 (s, 3H). **LRMS**: 390.1 (calc) 391.2 (found).	49
219	360		CH	CH	4-(5-Benzoylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide	**1H NMR (DMSO)** δ (ppm): 11.77 (s, 1H), 9.61 (s, 1H); 7.93 (d, J = 7.0 Hz, 4H), 7.52-7.63 (m, 3H), 7.38 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.89 (s, 2H), 4.15 (s, 2H), 2.24 (s, 3H). $(MH)^+$: 467.0	49
220	361		CH	CH	N-(2-Amino-phenyl)-4-[4-cyano-3-methyl-5-(3-phenyl-ureido)-thiophen-2-ylmethyl]-benzamide	**1H NMR (DMSO)** δ (ppm): 10.12 (s, 1H), 9.61 (s, 1H), 9.21 (s, 1H); 7.93 (d, J = 7.6 Hz, 2H), 7.27-7.43 (m, 6H), 7.16 (d, J = 7.6 Hz, 1H), 6.93-7.05 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H), 4.08 (s, 2H), 2.19 (s, 3H). $(MH)^+$: 482.4	49
221	362		CH	CH	N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamide	**^{1}H NMR: (DMSO)** δ (ppm): 9.60 (s, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92-7.04 (m, 5H), 6.75 (dd, J = 8.1 Hz, 1.1 Hz, 1H), 6.57 (td, J = 7.4 Hz, 1.4 Hz, 1H), 5.24 (s, 2H), 4.88 (bs, 2H); 4.82 (s, 2H). $(MH)^+$: 374.1	11

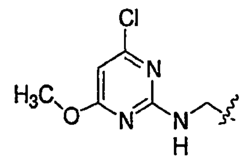
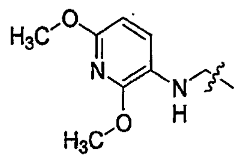
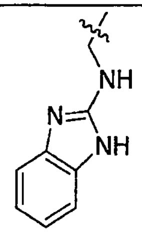
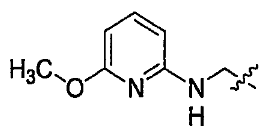
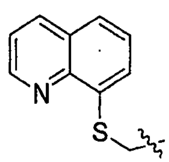
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
222	363		CH	CH	N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-ylmethyl)-benzamide	^{1}H NMR: (DMSO) δ (ppm): 9.58 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.19-7.11 (m, 3H), 7.04-6.92 (m, 2H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (td, J = 8.0 Hz, 1.6 Hz, 1H), 5.31 (s, 2H); 4.88 (bs, 2H); 3.70 (s, 2H). $(MH)^+$: 390.1	11
223	364		CH	CH	N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-pyrido[3,2-b][1,4]oxazin-4-ylmethyl)-benzamide	^{1}H NMR: (DMSO) δ (ppm): 9.57 (bs, 1H), 7.98 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.45-7.40 (m, 3H), 7.15 (d, J = 8.2 Hz, 1H), 7.09-7.05 (m, 1H), 6.96 (dd, J = 7.6, 7.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 7.6, 7.6 Hz, 1H), 5.31 (s, 2H), 4.90 (bs, 2H), 4.87 (s, 2H). $(MH)^+$: 375.1	11
224	365		CH	CH	N-(2-Amino-phenyl)-4-(1-hydroxy-3-oxo-indan-2-ylmethyl)-benzamide	^{1}H NMR: (DMSO) δ (ppm): 9.67 (s, 1H); 7.98 (d, J = 8.2 Hz, 2H), 7.73-7.84 (m, 3H), 7.53-7.62 (m, 3H), 7.24 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 5.27 (t, J = 6.4 Hz, 1H), 4.95 (s, 2H), 3.21-3.30 (m, 1H), 3.11-3.13 (m, 2H). $(MH)^+$: 373.1	46
225	366		CH	CH	N-(2-Amino-phenyl)-4-phenoxy-benzamide	^{1}**H NMR: (DMSO)** δ (ppm): 9.61 (s, 1H); 8.01 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.06-7.24 (m, 6H), 6.97 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H). $(MH)^+$: 305.0	1
226	367		CH	CH	*N*-(2-Amino-phenyl)-4-[5-(4-methoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzamide	^{1}**H NMR ($CDCl_3$)** δ (ppm): 8.77 (s,1H), 7.93 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38-6.98 (m, 6H), 6.91 (d, J = 8.4Hz, 2H), 6.09-5.98 (m, 4H), 3.81 (s, 3H).	52

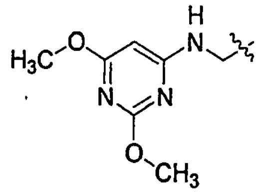
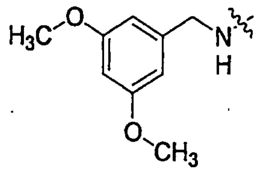
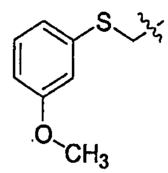
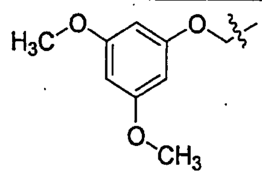
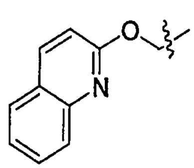
SUBSTITUTE SHEET (RULE 26)

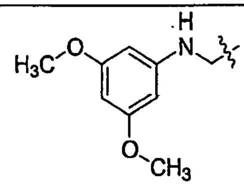
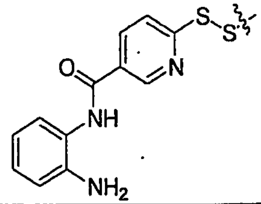
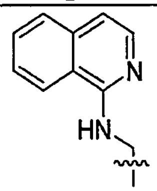
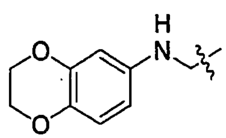
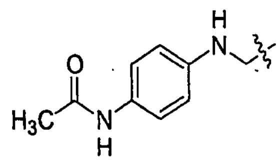
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
230	371		CH	CH	*N*-(2-Amino-phenyl)-4-[1,3-bis-(3,4-dimethoxy-phenyl)-ureidomethyl]-benzamide	**^{1}H NMR (DMSO-d$_6$):** δ 10.08 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.70 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39-7.33 (m, 1H), 7.30-6.90 (m, 7H), 6.87 (dd, J = 2.2, 8.35 Hz, 1H), 6.78 (dd, J = 2.2, 8.35 Hz, 1H), 5.01 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H).	57
231	372		CH	CH	*N*-(2-Amino-phenyl)-4-[3-(4-chloro-phenyl)-1-(3,4-dimethoxy-phenyl)-ureidomethyl]-benzamide	**^{1}H NMR (CDCl$_3$):** δ 8.02 (brs, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.42-7.24 (m, 6H), 7.16 (t, J = 7.5 Hz, 1H), 6.91 (brd, J = 5.71 Hz, 3H), 6.75 (brd, J = 8.3 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 4.99 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H).	57
232	373		CH	CH	*N*-(2-Amino-phenyl)-4-[1-(3,4-dimethoxy-phenyl)-3-phenyl-ureidomethyl]-benzamide	**^{1}H NMR (DMSO-d$_6$):** δ 10.10 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.80-7.72 (m, 1H), 7.50 (dd, J = 7.0, 5.7 Hz, 4H), 7.37 (d, J = 7.9 Hz, 1H), 7.30-6.94 (m, 7H), 6.78 (d, J = 6.6 Hz, 1H), 5.03 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H).	57
233	374		CH	CH	*N*-(2-Amino-phenyl)-4-[1-(3,4-dimethoxy-phenyl)-3-(4-phenoxy-phenyl)-ureidomethyl]-benzamide	**^{1}H NMR (CDCl$_3$):** δ 8.02 (brs, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 8.35 Hz, 2H), 7.43-7.32 (m, 5H), 7.10-7.30 (2m, 5H), 7.19-7.10 (m, 2H), 7.01 (dd, J = 8.35, 2.2 Hz, 3H), 6.94 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.8, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.34 (s, 2H), 5.02 (s, 2H), 3.98 (s, 3H), 3.87 (s, 3H).	57
234	375		CH	CH	Biphenyl-4,4'-dicarboxylic acid bis-[(2-amino-phenyl)-amide]	**^{1}H NMR (CD$_3$OD)** δ (ppm): 9.80 (bs, 2H), 8.16 (d, J=7.9 Hz, 4H), 7.96 (d, J= 7.9 Hz, 4H), 7.23 (d, J=7.4 Hz, 2H), 7.03 (dd, J=6.9, 7.4 Hz, 2H), 6.84 (d, J=8.2 Hz, 2H), 6.66 (dd, J=6.9, 7.7 Hz, 2H), 5.06 (bs, 4H).	15

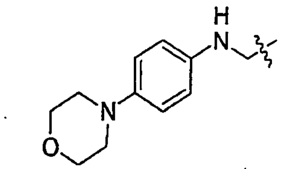
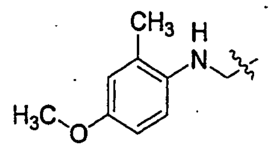
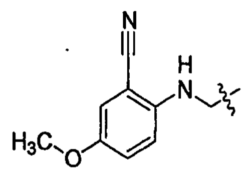
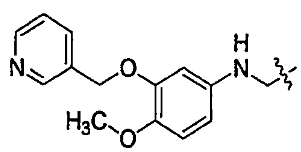
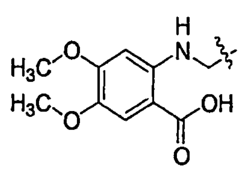
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
236	377		CH	CH	*N*-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.6 (bs, 1H), 8.32 (d, J=4.9 Hz, 2H), 7.97 (dt, J= 7.9, 9.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47, (d, J=8.2 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.01 (dt, J=7.4, 7.7 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H).	13
237	378		CH	CH	*N*-(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.61 (d, J= 7.9 Hz, 2H), 7.21 (d, J=7.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J=7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H).	11
238	379		CH	CH	*N*-(2-Amino-phenyl)-4-(4-trifluoromethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 9.07 (d, J=5.2 Hz, 1H), 7.97 (d, J=7.4 Hz, 2H), 7.78 (d, J=4.7 Hz, 1H), 7.63 (d, J=7.4 Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.01 (dt, J= 7.4, 7.7 Hz, 1H), 6.81 (d, J=8.2 Hz, 1H), 6.64 (dt, J=7.1, 7.4 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H).	11
239	380		N	CH	Pyridine-2,5-dicarboxylic acid bis-[(2-amino-phenyl)-amide]	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 10.23 (bs, 1H), 10.04 (bs, 1H), 9.30 (s, 1H), 8.62 (dd, J=1.8, 8.0 Hz, 1H), 8.30 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.4 Hz, 1H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=7.0, 14.0 Hz, 2H), 6.90-6.83 (m, 2H), 6.74-6.63 (m, 2H), 5.11 (bs, 4H).	1
240	381		CH	CH	*N*-(2-Amino-phenyl)-4-(pyridin-2-ylsulfanylmethyl)-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 8.52 (bs, 1H), 7.96 (d, J=7.4 Hz, 2H), 7.69 (d, J=5.8 Hz, 1H), 7.59 (d, J=7.4 Hz, 2H), 7.38 (d, J=7.7 Hz, 1H), 7.19 (bs, 2H), 7.00 (d, J=6.9 Hz, 1H), 6.83 (d, J=6.9 Hz, 1H), 6.64 (dd, J=6.7, 7.2 Hz, 1H), 4.94 (bs, 2H), 4.55 (b+s, 2H).	11

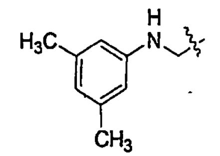
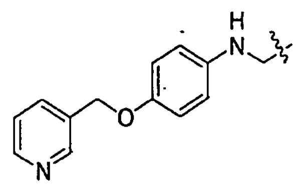
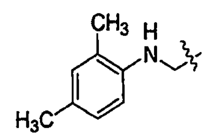
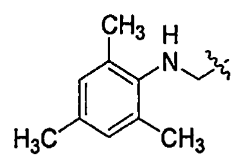
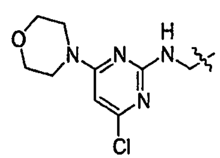
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
241	382		CH	CH	*N*-(2-Amino-phenyl)-4-[(4,6-dimethyl-pyrimidin-2-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*),** δ (ppm): 9.65 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H),7.57 (d, J=6.3 Hz, 1H), 7.47 (d, J= 7.7 Hz, 2H), 7.21 (d, J=7.4 Hz, 1H), 7.00 (d, J= 5.8 Hz, 1H), 6.59 (d, J=6.6 Hz, 1H), 6.64 (dd, J=6.0, 7.4 Hz, 1H), 5.01 (s, 2H), 4.61 (d, J=6.0 Hz, 2H), 2.24 (s, 6H).	33
242	383		CH	CH	*N*-(2-Amino-phenyl)-4-[(4,6-dimethyl-pyridin-2-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*),** δ (ppm): 9.66 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H),7.50 (d, J=8.2 Hz, 2H), 7.96 (d, J= 7.9 Hz, 1H), 7.01 (dd, J=7.7, 7.4 Hz, 1H), 6.82 (d, J= 7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.33 (s, 1H), 6.25 (s, 1H), 4.58 (d, J=4.4 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H).	33
243	384		CH	CH	*N*-(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-yloxymethyl)-benzamide	[1]**H-NMR (DMSO-*d6*),** δ (ppm): 9.58 (bs, 1H), 7.88 (d, J=5.8 Hz, 2H),7.46 (d, J=8.2 Hz, 2H), 6.90-6.81 (m, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.50 (t, J= 7.4 Hz, 1H), 6.40-6.38 (m, 1H), 6.29-6.26 (m, 1H), 5.33 (s, 2H), 2.25 (s, 6H).	11
244	385		CH	CH	N-(2-Amino-phenyl)-4-[(6-methoxy-pyrimidin-4-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*),** δ (ppm): 9.64 (bs, 1H), 8.21 (bs, 1H), 7.95 (d, J=7.96 Hz, 2H),7.83 (d, J=5.8 Hz, 1H), 7.44 (d, J=7.9Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.00 (dd, J= 7.4, 7.7 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.64 (d, J=7.1 Hz, 1H), 4.96 (bs, 2H), 4.58 (bs, 2H), 3.81 (s, 3H).	33
245	386		CH	CH	4-[(6-Acetyl-benzo[1,3]dioxol-5-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide	[1]**H-NMR (DMSO-*d6*),** δ (ppm): 9.79 (bs, 1H), 7.99 (d, J=8.5 Hz, 2H), 7.48 (d, J=7.96 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4Hz, 1H), 7.02 (dd, J=7.1, 7.7 Hz, 1H), 6.83 (d, J= 7.7 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.59 (bs, 2H), 2.52 (bs, 3H).	33

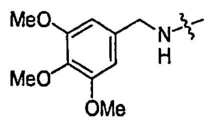
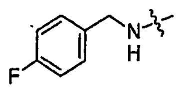
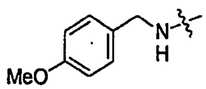
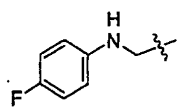
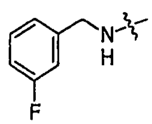
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
246	387		CH	CH	N-(2-Amino-phenyl)-4-[(4-chloro-6-methoxy-pyrimidin-2-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.47 (bs, 2H), 7.39 (bs, 1H), 7.19 (d, J=7.4Hz, 1H), 7.00 (dd, J=6.9, 7.4 Hz, 1H), 6.81 (d, J= 7.1 Hz, 1H), 6.63 (dd, J=7.7, 6.8 Hz, 1H), 6.10 (bs, 1H), 4.56 (d, J=6.0 Hz,, 2H), 3.83 (s, 3H).	33
247	388		CH	CH	N-(2-Amino-phenyl)-4-[(2,6-dimethoxy-pyridin-3-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.63 (bs, 1H), 7.94 (d, J=6.9 Hz, 2H), 7.47 (d, J=6.59 Hz, 2H), 7.15 (d, J= 7.9 Hz, 1H), 6.99 (dd, J=5.7, 7.4Hz, 1H), 6.80 (d, J= 7.8 Hz, 1H), 6.71 (d, J= 6.6 Hz, 1H), 6.62 (dd, J=7.7, 7.1 Hz, 1H), 6.15 (d, J=8.2 Hz, 1H), 4.96 (bs, 2H), 4.38 (bs, 2H), 3.94 (s, 3H), 3.75 (s, 3H).	33
248	389		CH	CH	N-(2-Amino-phenyl)-4-[(1H-benzoimidazol-2-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 10.9 (bs, 1H), 9.64 (bs, 1H), 7.99 (bs, 2H), 7.55 (bs, 2H), 7.21-7.17 (m, 3H), 7.14-6.81 (m, 4H), 6.64 (d, J= 6.0 Hz, 1H), 4.92 (bs, 2H), 4.65 (bs, 2H).	33
249	390		CH	CH	*N*-(2-Amino-phenyl)-4-[(6-methoxy-pyridin-2-ylamino)-methyl]-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.60 (bs, 1H), 7.96 (d, J=7.9 Hz, 1H), 7.52-7.50 (m, 2H), 7.37-7.30 (m, 1H), 7.25-7.21 (m, 2H), 7.19-6.99 (m, 1H), 6.84-6.81 (m, 1H), 6.67-6.64 (m, 1H), 6.11-6.07 (m, 1H), 5.93-5.89 (m, 1H), 4.93 (bs, 2H), 4.56 (d, J=5.8 Hz, 2H), 3.80 (s, 3H).	37
250	391		CH	CH	*N*-(2-Amino-phenyl)-4-(quinolin-8-ylsulfanylmethyl)-benzamide	[1]**H-NMR (DMSO-*d6*)**, δ (ppm): 9.68 (bs, 1H), 8.95 (bs, 2H), 8.43-8.38 (m, 1H), 7.90 (bs, 2H), 7.80-7.55 (m, 6H), 7.22 (d, J= 7.7 Hz, 1H), 7.03 (d, J= 7.7 Hz, 1H), 6.63 (d, J=7.4 Hz, 1H), 5.05 (bs, 2H), 4.48 (d, J=7.7, 2H).	11

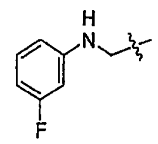
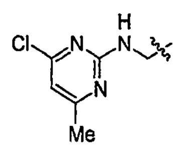
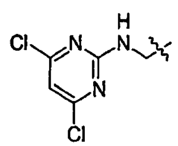
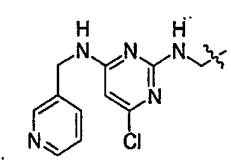
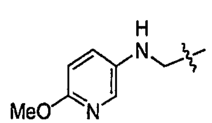
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
251	392		CH	CH	*N*-(2-Amino-phenyl)-4-[(2,6-dimethoxy-pyrimidin-4-ylamino)-methyl]-benzamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.84 (t, J=5.9 Hz, 1H), 7.46 (d, J=7.46 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.04 (d, J=6.6 Hz, 1H), 6.83 (d, J= 7.9 Hz, 1H), 6.64 (dd, J=7.7, 7.4 Hz, 1H), 5.51 (bs, 1H), 4.57 (bs,, 2H), 3.82 (s, 3H), 3.84 (s, 3H).	37
252	393		CH	CH	*N*-(2-Amino-phenyl)-4-(3;5-dimethoxy-benzylamino)-benzamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.63 (bs, 1H), 7.79 (d, J=8.5 Hz, 2H), 7.19 (d, J=6.6 Hz, 1H), 7.00 (dd, J=7.9, 7.1 Hz, 1H), 6.62 (t, J=6.0 Hz, 1H), 6.82 (dd, J=1.4, 7.9 Hz, 1H), 6.67 (d, J= 8.8 Hz, 2H), 6.58 (bs, 2H), 6.42 (bs, 1H), 4.87 (bs, 2H), 4.34 (d, J=6.0 Hz, 2H), 3.77 (s, 6H).	37
253	394		CH	CH	*N*-(2-Amino-phenyl)-4-(3-methoxy-phenylsulfanylmethyl)-benzamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.29-7.20 (m, 2H), 7.02-6.95 (m, 2H), 6.84-6.79 (m, 1H), 6.67-6.62 (m, 1H), 6.57-6.54 (m, 1H), 6.44-6.41 (m, 1H), 4.93 (bs, 2H), 4.41 (bs, 2H), 3.79 (s, 3H).	11
254	395		CH	CH	*N*-(2-Amino-phenyl)-4-(3,5-dimethoxy-phenoxymethyl)-benzamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.72 (bs, 1H), 8.05 (d, J=8.2 Hz, 2H), 7.61 (d, J=7.9 Hz, 2H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=6.9, 7.1 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (dd, J= 7.4, 7.7 Hz, 1H), 6.27 (s, 2H), 6.26 (s, 1H), 5.23 (s, 2H), 5.21 (bs, 2H), 3.77 (s, 6H).	11
255	396		CH	CH	*N*-(2-Amino-phenyl)-4-(quinolin-2-yloxymethyl)-benzamide	**^{1}H-NMR (DMSO-*d6*)**, δ (ppm): 9.70 (bs, 1H), 8.35 (d, J=9.1 Hz, 2H), 8.05 (d, J=7.9 Hz, 2H), 7.96 (d, J=7.9 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.76-7.69 (m, 2H), 7.51 (dd, J=6.9, 7.1 Hz, 1H), 7.24-7.16 (m, 2H), 7.02 (dd, J=6.9, 7.4 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.4 Hz, 1H), 5.66 (s, 2H), 4.94 (bs, 2H).	11

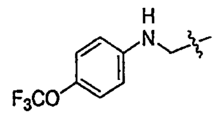
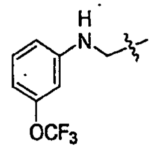
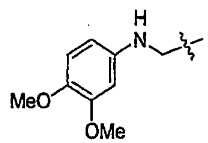
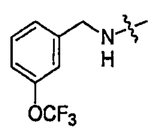
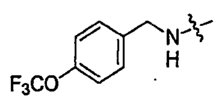
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
256	397		CH	CH	*N*-(2-Amino-phenyl)-4-[(3,5-dimethoxy-phenylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.62 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.49 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 7.00 (dd, J=7.5, 7.9 Hz, 1H), 6.81 (d, J=7.9 Hz, 1H), 6.63 (dd, J= 7.0, 8.0 Hz, 1H), 5.78 (s, 2H), 5.76 (s, 1H), 4.92 (bs,, 2H), 4.35 (d, J=5.7, 2H), 3.65 (s, 6H).	33
257	398		CH	N	bis(*N*-(2-Amino-phenyl)-nicotinamide)-6-disulfide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.82 (bs, 2H), 9.08 (bs, 2H), 8.34 (d, J=8.3 Hz, 2H), 7.83 (d, J=8.3 Hz, 2H), 7.18 (d, J=7.5 Hz, 2H), 7.01 (dd, J=6.3, 7.0 Hz, 2H), 6.80 (d, J=7.9 Hz, 2H), 6.61 (t, J=7.03 Hz, 2H), 5.05 (bs, 4H).	1
258	399		CH	CH	*N*-(2-Amino-phenyl)-4-(isoquinolin-1-ylaminomethyl)-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.90 (bs, 1H), 8.16 (bs, 2H), 7.65 (d, J=4.8 Hz, 2H), 7.54 (bs, 2H), 7.25 (d, J=7.0 Hz, 2H), 7.11 (bs, 2H), 7.07-7.02 (m, 2H), 6.84 (d, J=7.9 Hz, 1H), 6.67 (bs, 1H), 5.01 (bs, 2H), 4.88 (bs, 2H).	33
259	400		CH	CH	*N*-(2-Amino-phenyl)-4-[(2,3-dihydro-benzo[1,4]dioxin-6-ylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.0 Hz, 2H), 7.51 (d, J=7.0 Hz, 2H), 7.22 (d, J=7.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.84 (bs, 1H), 6.82-6.71 (m, 2H), 6.16 (d, J=6.6 Hz, 1H), 6.08 (s, 1H), 4.32 (bs, 2H), 4.16-4.13 (m, 4H).	33
260	401		CH	CH	4-[(4-Acetylamino-phenylamino)-methyl]-*N*-(2-amino-phenyl)-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.66 (bs, 1H), 9.56 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.53 (d, J=7.9 Hz, 2H), 7.28 (d, J=8.8 Hz, 2H), 7.22 (d, J=7.9 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.65 (t, J=7.5 Hz, 1H), 6.55 (d, J=8.3 Hz, 2H), 4.98 (bs, 2H), 4.38 (bs, 2H), 2.00 (s, 3H).	33

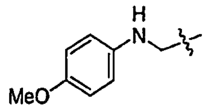
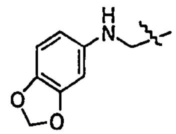
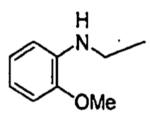
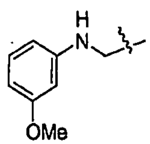
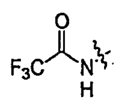
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
261	402		CH	CH	*N*-(2-Amino-phenyl)-4-[(4-morpholin-4-yl-phenylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.65 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.52 (d, J=7.9 Hz, 2H), 7.21 (d, J=7.5 Hz, 1H), 7.02 (dd, J=7.0, 7.9 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.78 (d, J=8.8 Hz, 2H), 6.64 (t, J=7.5 Hz, 1H), 6.55 (d, J=8.8 Hz, 2H), 4.94 (bs, 2H), 4.35 (d, J=5.7 Hz, 2H), 3.74 (t, J=4.4 Hz, 4H), 2.92 (t, J=4.4 Hz, 4H).	33
262	403		CH	CH	*N*-(2-Amino-phenyl)-4-[(4-methoxy-2-methyl-phenylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.64 (bs, 1H), 7.96 (d, J=7.6 Hz, 2H), 7.52 (d, J=7.6 Hz, 2H), 7.21 (d, J=8.2 Hz, 1H), 7.02 (t, J=8.2, 7.0 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 6.71-6.53 (m, 3H), 6.32-6.30 (m, 1H), 4.94 (bs, 2H), 4.45 (d, J=5.9 Hz, 2H), 3.65 (s, 3H), 2.23 (s, 3H).	33
263	404		CH	CH	*N*-(2-Amino-phenyl)-4-[(2-cyano-4-methoxy-phenylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.65 (bs, 1H), 7.98 (d, J=7.4 Hz, 2H), 7.56 (d, J=7.5 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 6.99 (d, J= 7.5 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.63 (t, J=6.6 Hz, 2H), 6.27 (s, 1H), 4.93 (bs, 2H), 4.55 (d, J=5.3 Hz, 2H), 3.69 (s, 6H).	33
264	405		CH	CH	*N*-(2-Amino-phenyl)-4-{[4-methoxy-3-(pyridin-3-ylmethoxy)-phenylamino]-methyl}-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.62 (s, 1H), 8.72 (s, 1H), 8.49 (d, J =10.1 Hz, 1H), 7.93 (d, J =7.9 Hz, 2H), 7.68 (d, J = 6.6 Hz, 1H), 7.37 (d, J = 7.5 Hz, 2H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J =7.9 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.62 (d, J=7.5 Hz, 1H), 6.23 (d, J =2.6 Hz, 1H), 6.09 (J=8.8 Hz, 1H), 5.76 (s, 1H), 4.64 (bs, 4H), 3.62 (s, 3H).	33
265	406		CH	CH	2-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-4,5-dimethoxy-benzoic acid	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.67 (bs, 1H), 8.00 (d, J=7.9 Hz, 2H), 7.54 (d, J=7.9 Hz, 2H), 7.34 (s, 1H), 7.20 (d, J= 7.9 Hz, 2H), 7.0 (t, J=7.9 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.62 (t, J=7.9 Hz, 1H), 6.31 (s, 1H), 4.95 (bs, 2H), 4.62 (bs, 2H), 3.75 (s, 3H), 3.70 (s, 3H).	33

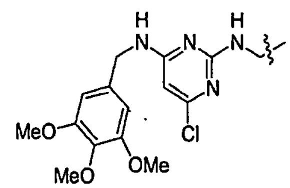
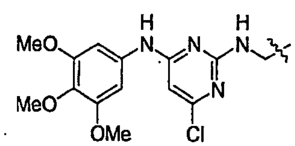
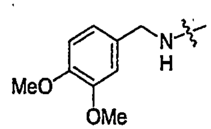
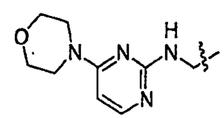
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
266	407		CH	CH	*N*-(2-Amino-phenyl)-4-[(3,5-dimethyl-phenylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.60 (s, 1H), 7.93 (d, J=7.9 Hz, 2H), 7.45 (d, J=7.9 Hz, 2 H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J= 7.5 Hz, 1H), 6.78 (d, J=7.9 Hz, 1H), 6.58 (t, J= 7.0 Hz, 1H), 6.19-6.17 (m, 3H), 4.88 (s, 2H), 4.32 (d, J=5.7 Hz, 2H), 2.10 (s, 6H).	33
267	408		CH	CH	*N*-(2-Amino-phenyl)-4-{[4-(pyridin-3-ylmethoxy)-phenylamino]-methyl}-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.65 (s, 1H), 8.72 (s, 1H), 8.54 (s, 1H), 8.49 (d, J=10.9 Hz, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.71 (d, J=7.9 Hz, 1H), 7.44 (d, J=8.3 Hz, 2H), 7.41-7.36 (m, 1H), 7.20 (d, J=7.9 Hz, 1H), 7.00 (t, J= 7.4 Hz, 1H), 6.83 (d, J=7.0 Hz, 1H), 6.70-6.60 (m, 4H), 4.62 (s, 4H).	33
268	409		CH	CH	*N*-(2-Amino-phenyl)-4-[(2,4-dimethyl-phenylamino)-methyl]-benzamide	^{1}**H-NMR (DMSO-*d6*)**, δ (ppm): 9.58 (s, 1H), 7.90 (d, J=7.9 Hz, 2H), 7.45 (d, J=7.5 Hz, 2H), 7.15 (d, J=7.5 Hz, 1H), 6.96 (t, J=7.5 Hz, 1H), 6.79 (s, 1H), 6.76 (d, J=9.6 Hz, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.59 (t, J=7.0 Hz, 1H), 6.22 (d, J=7.9 Hz, 1H), 4.89 (bs, 2H), 4.39 (d, J=5.7 Hz, 2H), 2.15 (s, 3H), 2.10 (s, 3H).	33
269	410		CH	CH	*N*-(2-Amino-phenyl)-4-[(2,4,6-trimethyl-phenylamino)-methyl]-benzamide	^{1}**H-NMR (CD_3OD)**, δ (ppm): 7.91 (d, J=7.9 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.18 (d, J=7.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.92 (d, J=7.9 Hz, 1H), 6.77 (s, 3H), 4.15 (bs, 2H), 2.19 (s, 9H).	33
270	411		CH	CH	*N*-(2-Amino-phenyl)-4-[(4-chloro-6-morpholin-4-yl-pyrimidin-2-ylamino)-methyl]-benzamide	^{1}**H NMR (300 MHz, DMSO-D_6)** δ *** (ππμ): 9.66 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.82 (m, 1H), 7.47 (d, J = 7.7 Hz, 2H), 7.21 (d, J = 8.2 Hz, 1H), 7.03 (dd, J = 7.1, 7.1 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.65 (dd, J = 7.4, 7.4 Hz, 1H), 6.17(bs, 1H), 4.94 (s, 2H, NH_2), 4.53 (d, J = 5.8 Hz, 2H), 3.58 (m, 4H), 3.62 (m, 4H).	24, 33

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
271	412		CH	CH	N-(2-Amino-phenyl)-4-(3,4,5-trimethoxy-benzylamino)-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.33 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.99 (m, 1H), 6.87 (dd, J = 6.0, 5.8Hz, 1H), 6.82 (m, 1H), 6.77 (s, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.64 (m, 1H), 4.87 (s, 2H, NH$_2$), 4.32 (d, J = 5.5 Hz, 2H), 3.81 (s, 6H), 3.79 (s, 3H).	33
272	413		CH	CH	N-(2-Amino-phenyl)-4-(4-fluoro-benzylamino)-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.45 (dd, J = 5.8, 8.5 Hz, 2H), 7.21 (m, 3H), 6.91 (m, 2H), 6.81 (dd, J = 1.1, 8.0Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.62 (dd, J = 1.0, 7.2 Hz, 1H), 4.86 (s, 2H, NH$_2$), 4.39 (d, J = 6.0 Hz, 2H).	33
273	414		CH	CH	N-(2-Amino-phenyl)-4-(4-methoxy-benzylamino)-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.31 (s, 1H), 7.79 (dd, J = 1.1, 8.5 Hz, 2H), 7.33 (d, J = 7.1 Hz, 2H), 7.19 (d, J =7.7 Hz, 1H), 6.97 (m, 3H), 6.84 (m, 2H), 6.65 (m, 3H), 4.86 (s, 2H, NH$_2$), 4.33 (d, J = 5.5 Hz, 2H), 3.58 (d, J = 1.6 Hz,3H).	33
274	415		CH	CH	N-(2-Amino-phenyl)-4-[(4-fluoro-phenylamino)-methyl]-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.02 (ddd J =1.6, 7.1, 8.2 Hz, 1H), 6.93 (dd, J =8.8, 9 Hz, 2H), 6.83 (dd, J =1.1, 8.0 Hz, 1H), 6.63 (m, 3H), 6.35 (t, J= 6.2 Hz, 1H), 4.94 (s, 2H, NH$_2$), 4.38 (d, J = 6.3 Hz, 2H).	33
275	416		CH	CH	N-(2-Amino-phenyl)-4-(3-fluoro-benzylamino)-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.32 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.44 (m, 1H), 7.26 (m, 1H), 7.18 (dd, J = 1.4, 8.0 Hz, 2H), 7.12 (ddd, J =1.7, 8.0, 8.2 Hz, 1H), 6.99 (m, 2H), 6.81 (dd, J =1.4, 8.0 Hz, 1H), 6.67 (dd, J = 1.6, 8.8 Hz, 2H), 6.62 (dd, J= 1.4, 7.4 Hz, 1H), 4.87 (s, 2H, NH$_2$), 4.45 (d, J = 6.0 Hz, 2H).	33

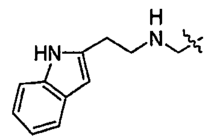
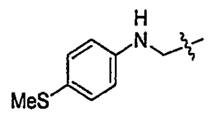
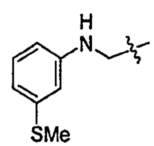
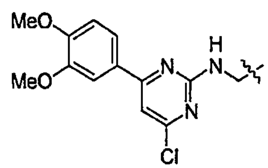
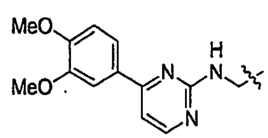
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
276	417		CH	CH	N-(2-Amino-phenyl)-4-[(3-fluoro-phenylamino)-methyl]-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 6.99-7.14 (m,2H), 6.83 (d, J = 8.0 Hz, 1H), 6.76 (m, 1H), 6.64 (dd, J =7.4, 7.4 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.34 (m, 2H), 4.94 (s, 2H, NH_2), 4.41 (d, J = 6.0 Hz, 2H).	33
277	418		CH	CH	N-(2-Amino-phenyl)-4-[(4-chloro-6-methyl-pyrimidin-2-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-D$_6$)** δ **(ppm): 9.66 (s, 1H),** 8.23 (m, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 (ddd, J = 1.5, 7.1, 8.0 Hz, 1H), 6.83 (dd, J = 1.5, 8.1 Hz, 1H), 6.65 (m, 2H), 4.94 (s, 2H, NH_2), 4.61 (m, 2H), 2.3 2(s, 3H).	33
278	419		CH	CH	N-(2-Amino-phenyl)-4-[(4,6-dichloro-pyrimidin-2-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-D$_6$)** δ **(ppm): 9.69 (s, 1H),** 8.82 (m, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 7.0 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 8.2Hz, 1H), 6.67 (m, 1H), 5.0 (bs, 2H, NH_2), 4.60 (d, J = 6.3 Hz, 2H).	33
279	420		CH	CH	N-(2-Amino-phenyl)-4-({4-chloro-6-[(pyridin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-methyl)-benzamide	[1]**H NMR (300 MHz, DMSO-D$_6$)** δ **(ppm): 9.87 (s, 1H),** 8.49 (bs, 2H), 7.26-8.02 (bm, 8H), 7.22 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 7.4, 7.4 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.1, 8.0 Hz, 1H), 5.86 (bs, 1H), 4.95 (s, 2H, NH_2), 4.51 (m, 2H).	24, 33
280	421		CH	CH	N-(2-Amino-phenyl)-4-[(6-methoxy-pyridin-3-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-D$_6$)** δ **(ppm): 9.66 (s, 1H),** 7.99 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 7.5 Hz, 7.9 Hz, 1H), 7.12 (dd, J = 3.08 Hz, 8.79 Hz, 1H), 7.02 (dd, J = 7.0 Hz, 7.5 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (m, 2H), 6.15 (t, J = 6.16 Hz, 1H), 4.94 (s, 2H, NH_2), 4.39 (d, J = 6.15 Hz, 2H), 3.75 (s, 3H).	33

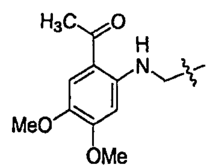
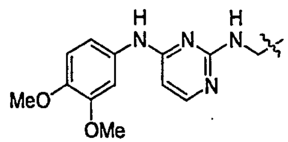
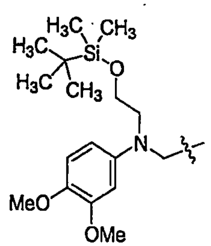
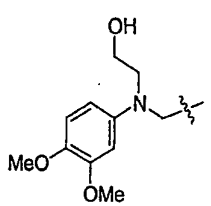
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
281	422		CH	CH	N-(2-Amino-phenyl)-4-[(4-trifluoromethoxy-phenylamino)-methyl]-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 9.1 Hz, 2H), 7.03 (dd, J = 7.1, 8.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.71 (t, J = 6.0 Hz, 1H), 6.63-6.67 (m, 3H), 4.94 (s, 2H, NH_2), 4.42 (d, J = 6.0 Hz, 2H).	33
282	423		CH	CH	N-(2-Amino-phenyl)-4-[(3-trifluoromethoxy-phenylamino)-methyl]-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.67 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.19 (m, 2H), 7.03 (ddd, J = 1.5, 8.0, 8.8 Hz, 1H), 6.85 (m, 2H), 6.63 (m, 2H), 6.55 (s, 1H), 6.50 (m, 1H), 4.94 (s, 2H, NH_2), 4.44 (d, J = 6.0 Hz, 2H).	33
283a	424b		CH	CH	N-(2-Amino-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.9 Hz, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.49 Hz, 7.49 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NH_2), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).	33
284	425		CH	CH	N-(2-Amino-phenyl)-4-(3-trifluoromethoxy-benzylamino)-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.31 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.45-7.56 (m, 2H), 7.39 (s, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 6.6 Hz, 1H), 6.96-7.03 (m, 2H), 6.81 (d, J = 6.9 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 7.7 Hz, 1H), 4.86 (s, 2H, NH_2), 4.48 (d, J = 5.8 Hz, 2H).	33
285	426		CH	CH	N-(2-Amino-phenyl)-4-(4-trifluoromethoxy-benzylamino)-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 1.4, 7.7 Hz, 1H), 6.99 (ddd, J = 1.4, 8.0, 8.5 Hz, 2H), 6.81 (dd, J = 1.4, 8.0, 1H), 6.68 (d, J = 8.8 Hz, 2H), 4.85 (s, 2H, NH_2), 4.45 (d, J = 6.0 Hz, 2H).	33

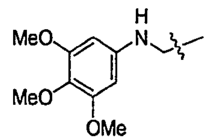
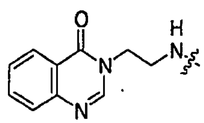
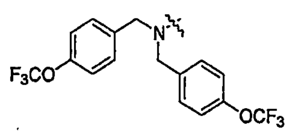
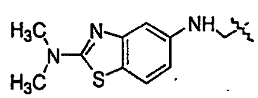
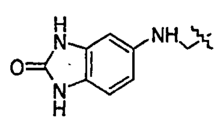
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
286	427		CH	CH	N-(2-Amino-phenyl)-4-[(4-methoxy-phenylamino)-methyl]-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.64 (s, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 1.4, 8.0 Hz, 1H), 7.02 (ddd, J = 1.4, 7.4, 8.0 Hz, 1H), 6.83 (dd, J = 1.4, 8.0 Hz, 1H), 6.74 (m, 2H), 6.65 (ddd, J = 1.4, 7.7, 8.8 Hz, 1H), 6.58 (m, 2H), 5.99 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH_2), 4.36 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H).	33
287	428		CH	CH	N-(2-Amino-phenyl)-4-(benzo[1,3]dioxol-5-ylaminomethyl)-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.0, 7.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.63-6.69 (m, 2H), 6.33 (d, J = 2.2 Hz, 1H), 6.15 (t, J = 6.16 Hz, 1H), 6.04 (dd, J = 2.2, 8.4 Hz, 1H), 5.86 (s, 2H), 4.94 (s, 2H, NH_2), 4.35 (d, J = 6.16 Hz, 2H).	33
288	429		CH	CH	N-(2-Amino-phenyl)-4-[(2-methoxy-phenylamino)-methyl]-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.63 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (ddd, J = 1.4, 7.1, 8.0 Hz, 1H), 6.86 (m, 2H), 6.56-6.75 (m, 3H), 6.43 (dd, J = 1.6, 7.7 Hz, 1H), 5.75 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH_2), 4.47 (d, J = 6.3 Hz, 2H), 3.88 (s, 3H).	33
289	430		CH	CH	N-(2-Amino-phenyl)-4-[(3-methoxy-phenylamino)-methyl]-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.61 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (dd, J = 1.1, 7.7 Hz, 1H), 6.97-7.05 (m, 2H), 6.82 (dd, J = 1.2, 8.1 Hz, 1H), 6.46 (ddd, J = 1.4, 7.7, 8.0 Hz, 1H), 6.41 (t, J = 6.3 Hz, 1H), 6.16-6.25 (m, 3H), 4.93 (s, 2H, NH_2), 4.39 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H).	33
290	431		CH	CH	N-(2-Amino-phenyl)-4-(2,2,2-trifluoro-acetylamino)-benzamide	^{1}**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 11.53 (s, 1H), 9.71 (s, 1H), 8.08 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.0, 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.0, 7.6 Hz, 1H), 4.96 (s, 2H, NH_2).	14

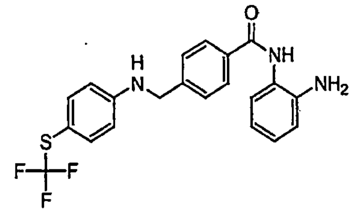
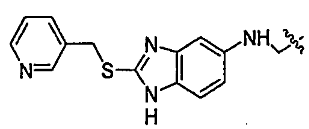
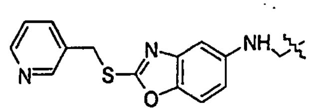
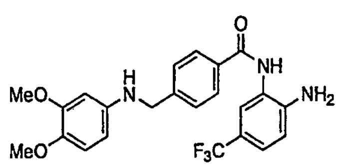
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
291	432		CH	CH	N-(2-Amino-phenyl)-4-{[4-chloro-6-(3,4,5-trimethoxy-benzylamino)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.64 (s, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.70 (bs, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.03 (dd, J = 7.0, 7.5 Hz, 1H), 6.84 (d, J = 7.9, Hz, 1H), 6.60-6.72 (m, 3H), 5.87 (s, 1H), 4.93 (s, 2H, NH$_2$), 4.54 (d, J = 6.2 Hz, 2H), 4.43 (bs, 2H), 3.78 (s, 6H), 3.68 (s, 3H).	24, 33
292	433		CH	CH	N-(2-Amino-phenyl)-4-{[4-chloro-6-(3,4,5-trimethoxy-phenylamino)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.65 (s, 1H), 9.43 (s, 1H), 7.97 (m, 3H), 7.46 (bs, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (m, 3H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.08 (s, 1H), 4.93 (s, 2H, NH$_2$), 4.69 (bs, 2H), 3.65 (s, 9H).	24, 33
293	434		CH	CH	N-(2-Amino-phenyl)-4-(3,4-dimethoxy-benzylamino)-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.04 (s, 1H), 6.92-7.01 (m, 3H), 6.80-6.87 (m, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.62 (m, 1H), 4.87 (s, 2H, NH$_2$), 4.32 (d, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H).	33
294	435		CH	CH	N-(2-Amino-phenyl)-4-[(4-morpholin-4-yl-pyrimidin-2-ylamino)-methyl]-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.64 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.31 (bs, 1H), 7.21 (d, J = 7.5, 1H), 7.02 (dd, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J= 7.0, 7.0 Hz,1H), 6.09 (d, J = 6.2 Hz, 1H), 4.94 (s, 2H, NH$_2$), 4.54 (d, J = 5.7 Hz, 2H), 3.67 (s, 4H), 3.53 (s, 4H).	24, 1, 33

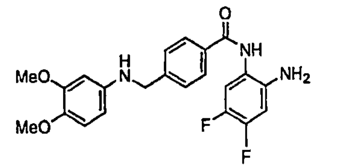
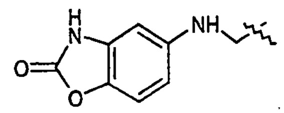
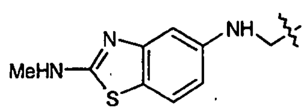
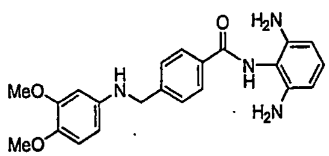
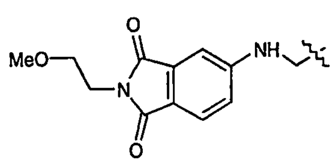
SUBSTITUTE SHEET (RULE 26)

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
295	436		CH	CH	N-(2-Amino-phenyl)-4-{[2-(1H-indol-3-yl)-ethylamino]-methyl}-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 10.82 (s, 1H), 9.65 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.18-7.23 (m, 2H), 7.11 (dd, J = 7.0, 8.0 Hz, 1H), 7.01 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.51 (dd, J = 7.5, 6.6 Hz, 1H), 4.93 (s, 2H, NH_2), 3.89 (s, 2H), 2.89 (m, 4H).	57
296	437		CH	CH	N-(2-Amino-phenyl)-4-[(4-methylsulfanyl-phenylamino)-methyl]-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.67 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2 H), 7.03 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.53 (m, 4H), 4.95 (s, 2H, NH_2), 4.41 (d. J = 5.7 Hz, 2H), 2.37 (s, 3H).	33
297	438		CH	CH	N-(2-Amino-phenyl)-4-[(3-methylsulfanyl-phenylamino)-methyl]-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.03 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.39-6.51 (m, 4H), 4.94 (s, 2H, NH_2), 4.41 (d. J = 5.7 Hz, 2H), 2.42 (s, 3H).	33
298	439		CH	CH	N-(2-Amino-phenyl)-4-{[4-chloro-6-(3,4-dimethoxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]**H NMR** (300 MHz, **DMSO-d$_6$**) δ (ppm): 9.66 (s, 1H), 8.37 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.68-7.79 (m, 2H), 7.55 (bs, 2H), 7.37 (s, 1H), 7.20 (d, J = 7.1 Hz, 1H), 7.11 (bs, 1H), 7.02 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (dd, J = 7.5, 7.5 Hz, 1H), 4.93 (s, 2H, NH_2), 4.86 (s, 2H), 3.88 (s, 6H).	15, 33
299	440		CH	CH	N-(2-Amino-phenyl)-4-{[4-(3,4-dimethoxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]**H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 9.64 (s, 1H), 8.35 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.89 (m, 1H), 7.72 (m, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.2 (d, J = 5.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.01 (m, 1H), 6.82 (d, J = 7.0 Hz, 1H), 6.41 (t, J = 7.5 Hz, 1 H), 4.92 (s, 2H, NH_2), 4.68 (d, J = 6.2 Hz, 2H), 3.82 (s, 6H).	15, 1, 33

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
300	441		CH	CH	4-[(2-Acetyl-4,5-dimethoxy-phenylamino)-methyl]-N-(2-amino-phenyl)-benzamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.68 (s, 1H), 9.45 (t, J = 5.7 Hz, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 6.6, 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.31 (s, 1H), 4.95 (s, 2H, NH_2), 4.63 (d, J = 5.7 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H).	33
301	442		CH	CH	N-(2-Amino-phenyl)-4-{[4-(3,4-dimethoxy-phenylamino)-pyrimidin-2-ylamino]-methyl}-benzamide	**^{1}H NMR (300 MHz, CD_3OD+$CDCl_3$)** δ (ppm): 7.99 (d, J = 7.9 Hz, 2H), 7.80 (d, J = 6.2 Hz, 1H), 7.76 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.27 (m, 1H), 7.14 (m, 1H), 7.05 (dd, J = 2.2, 8.8 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.08 (d, J = 6.2 Hz, 1H), 4.75 (s, 2H), 3.79 (s, 3H), 3.42 (s, 3H).	1, 33
302	443		CH	CH	N-(2-Amino-phenyl)-4-{[[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(3,4-dimethoxy-phenyl)-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.66 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.02 ((dd, J = 6.6, 8.4 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.0 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.19 (dd, J = 2.6, 8.8 Hz, 1H), 4.93 (s, 2H), 4.67 (s, 2H), 3.88 (t, J = 5.7 Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.60 (t, J = 5.5 Hz), 0.96 (s, 9H), 0.06 (s, 6H).	33
303	444		CH	CH	N-(2-Amino-phenyl)-4-{[(3,4-dimethoxy-phenyl)-(2-hydroxy-ethyl)-amino]-methyl}-benzamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm)δ (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 ((dd, J = 7.0, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.44 (s, 1H), 6.19 (d, J = 8.8 Hz, 1H), 4.94 (s, 2H), 4.79 (m, 1H), 4.66 (s, 2H), 3.67 and 3.71 (2s and broading underneath, 8H), 3.55 (m, 2H).	33, 23

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
304	445		CH	N	N-(2-Amino-phenyl)-6-[(3,4,5-trimethoxy-phenylamino)-methyl]-nicotinamide	[1]**H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 9.82 (s, 1H), 9.13 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 ((dd, J = 7.4, 7.7 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.40 (dd, J = 7.4, 7.7 Hz, 1H), 6.31 (t, J = 5.8 Hz, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.48 (d, J = 5.8 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H).	33
305	446		CH	N	N-(2-Amino-phenyl)-6-[2-(4-oxo-4H-quinazolin-3-yl)-ethylamino]-nicotinamide	[1]**H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 8.69 (d, J = 2.2 Hz, 1H), 8.46 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.32-8.36 (m, 1H), 7.91-7.96 (m, 1H), 7.77 (m, 1H), 7.67 (m, 1H) 7.5 (m, 4H), 7.2 (s, 1H), 4.46 (t, J = 5.9 Hz, 1H), 4.09 (t, J = 5.9 Hz, 2H).	3
306	447		CH	CH	N-(2-Amino-phenyl)-4-[bis-(3-trifluoromethoxy-benzyl)-amino]-benzamide	[1]**H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 9.37 (s, 1H), 7.84 (d J = 8.8 Hz, 2H), 7.54 (dd, J = 7.9, 7.9 Hz, 2H), 7.18-7.37 (m, 6H), 7.17 (d, J = 7.0 Hz, 1H), 6.99 (dd, J = 7.0, 7.9 Hz, 1H), 6.82 (m, 3H), 6.63 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (s, 4H), 4.86 (s, 2H).	33
307	448		CH	CH	N-(2-Amino-phenyl)-4-[(2-dimethylamino-benzothiazol-5-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 9.58 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.44 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 5.7 Hz, 1H), 4.88 (bs, 2H), 4.37 (d, J = 5.7 Hz, 2H), 3.06 (s, 6H).	33
308	449		CH	CH	N-(2-Amino-phenyl)-4-[(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 10.2 (s, 1H), 10.1 (s, 1H), 9.62 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 8.4 Hz, 1H), 6.30 (s, 1H), 4.89 (bs, 2H), 4.72 (s, 2H).	33

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
309	450		CH	CH	N-(2-Amino-phenyl)-4-[(4-trifluoromethylsulfanyl-phenylamino)-methyl]-benzamide	**^{1}H NMR (300 MHz, DMSO-d$_6$)** δ (ppm): 9.60 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 6.2 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 7.9 Hz, 1H), 4.88 (bs, 2H), 4.72 (d, J = 6.2 Hz, 2H).	33
310	451		CH	CH	N-(2-Amino-phenyl)-4-{[2-(pyridin-3-ylmethylsulfanyl)-1H-benzoimidazol-5-ylamino]-methyl}-benzamide	**^{1}H NMR (300 MHz, CD$_3$OD)** δ (ppm): 8.67 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 1.3, 4.4 Hz, 1H), 8.08 (s, 1H), 8.03 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.36-7.30 (m, 3H); 7.20-7.15 (m, 1H); 7.08 (dt, J = 1.3, 8.4 Hz, 1H), 6.94 (dd, J = 1.3, 7.9 Hz, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.65 (d, J = 1.8 Hz, 1H), 4.55 (s, 2H); 4.20 (bs, 2H); 3.36 (s, 2H).	33
311	452		CH	CH	N-(2-Amino-phenyl)-4-{[2-(pyridin-3-ylmethylsulfanyl)-benzooxazol-5-ylamino]-methyl}-benzamide	**^{1}H NMR (300 MHz, CD$_3$OD)** δ (ppm): 8.60 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.87 (m, 1H); 7.47 (d, J = 7.9 Hz, 2H), 7.30 (t, J = 6.6 Hz, 1H), 7.20-7.15 (m, 2H); 7.04 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.66 (s, 1H); 6.61 (d, J = 8.8 Hz, 1H), 4.87 (s, 2H); 4.45 (s, 2H); 4.37 (s, 2H); 3.35 (s, 2H).	33
312	453				N-(2-Amino-5-trifluoromethyl-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR** (300 MHz, **CDCl$_3$**) δ (ppm): 8.21 (s, 1H); 7.90 (d, J = 8.4 Hz, 2H); 7.54 (m, 1H); 7.50 (d, J = 8.4 Hz, 2H); 7.41-7.34 (m, 2H); 6.87 (d, J = 8.4 Hz, 1H); 7.77 (d, J = 8.4 Hz, 1H); 6.35 (d, J = 2.2 Hz, 1H); 6.20 (dd, J = 2.2, 8.8 Hz, 1H); 4.43 (s, 2H); 4.29 (s, 2H); 3.84 (s, 6H).	33

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
313	454				N-(2-Amino-4,5-difluoro-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR** (300 MHz, **$CDCl_3$**) δ (ppm): 8.21 (s, 1H); 7.84 (d, J = 7.9 Hz, 2H); 7.45 (d, J = 7.9 Hz, 2H); 7.20 (dd, J = 2.6, 8.4 Hz, 1H); 6.76 (d, J = 8.8 Hz, 1H); 6.57 (dd, J = 3.9, 7.9 Hz, 1H); 6.32 (d, J = 2.6 Hz, 1H); 6.16 (dd, J = 2.6, 8.4 Hz, 1H); 4.40 (s, 2H); 3.82 (s, 9H).	33
314	455		CH	CH	N-(2-Amino-phenyl)-4-[(2-oxo-2,3-dihydro-benzooxazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.60 (s, 1H); 7.93 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); 7.16 (d, J = 7.5 Hz, 1H); 6.97 (m, 2H); 6.78 (d, J = 7.5 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.35 (t, J = 5.7 Hz, 1H); 6.27 (m, 2H); 4.88 (bs, 2H); 4.34 (d, J = 6.2 Hz, 2H).	33
315	456		CH	CH	N-(2-Amino-phenyl)-4-[(2-methylamino-benzothiazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 7.92 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 4.4 Hz, 1H), 7.49 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 6.53 (s, 1H),); 6.40 (dd, J = 1.3, 8.4 Hz, 1H); 6.28 (t, J = 5.7 Hz, 1H), 4.88 (bs, 2H), 4.36 (d, J = 5.7 Hz, 2H), 2.85 (d, J = 4.4 Hz, 3H).	33
316	457				N-(2,6-Diamino-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR** (300 MHz, **$CDCl_3$**) δ (ppm): 8.09 (s, 1H); 7.88 (d, J = 7.5 Hz, 2H); 7.48 (d, J = 7.5 Hz, 2H); 6.97 (d, J = 7.9 Hz, 1H); 6.73 (d, J = 8.4 Hz, 2H); 6.64 (d, J = 7.9 Hz, 1H); 6.29 (s, 1H); 6.14 (d, J = 8.4 Hz, 1H); 4.39 (s, 2H); 3.81 (s, 3H); 3.80 (s, 3H); 3.70 (bs, 5H) .	33
317	458		CH	CH	N-(2-Amino-phenyl)-4-{[2-(2-methoxy-ethyl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-ylamino]-methyl}-benzamide	**^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.61 (s, 1H); 7.95 (d, J = 7.9 Hz, 2H); 7.73 (t, J = 5.7 Hz, 1H); 7.52 (d, J = 8.4 Hz, 1H); 7.47 (d, J = 7.9 Hz, 2H); 7.15 (d, J = 7.9 Hz, 1H); 6.97 (d, J = 7.5 Hz, 1H); 6.92 (bs, 1H); 6.86 (d, J = 8.4 Hz, 1H); 6.77 (d, J = 7.9 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 4.89 (bs, 2H); 4.54 (d, J = 5.7 Hz, 2H); 3.65 (t, J = 5.3 Hz, 2H); 3.47 (t, J = 5.3 Hz, 2H); 3.20 (s, 3H);	33

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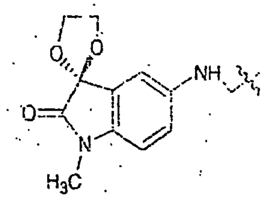
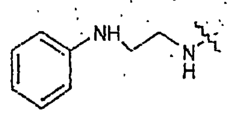
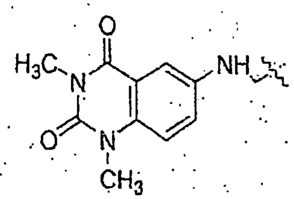
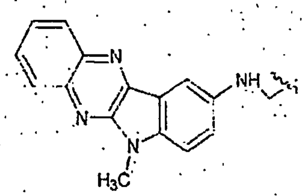
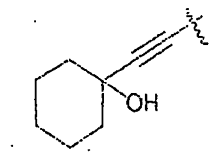
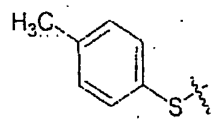
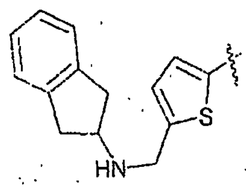
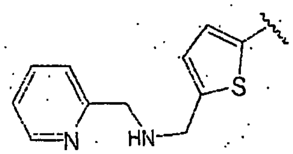
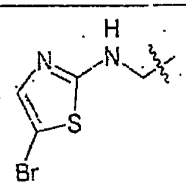
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
318	459		CH	CH	N-(2-Amino-phenyl)-4-{(3-spiro[1',2']dioxolane-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-ylamino)-methyl}-benzamide	[1]**H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.59 (s, 1H); 7.92 (d, J = 8.3 Hz, 2H); 7.46 (d, J = 8.3 Hz, 2H); 7.15 (d, J = 7.5 Hz, 1H); 6.96 (t, J = 7.0 Hz, 1H); 6.78-6.71 (m, 3H); 6.62-6.54 (m, 2H); 6.26 (t, J = 7.5 Hz, 1H); 4.87 (s, 2H); 4.36-4.32 (m, 4H); 4.23-4.19 (m, 2H); 2.98 (s, 3H).	33
319	460		CH	N	N-(2-Amino-phenyl)-6-(2-phenylamino-ethylamino)-nicotinamide	[1]**H NMR (300 MHz, CD_3OD)** δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 2.5, 8.9 Hz, 1H), 7.58 (m, 1H); 7.51 (m, 1H); 7.15 (dd, J = 1.1, 7.7 Hz, 1H), 7.08 (m, 2H); 6.89 (dd, J = 1.4, 8.0 Hz, 1H), 6.76 (dt, J = 4.4, 7.7 Hz, 1H), 6.67 (d, J = 7.7 Hz, 2H), 6.60 (m, 2H); 4.87 (bs, 2H); 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H).	33
320	461		CH	CH	N-(2-Amino-phenyl)-4-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-6-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.59 (s, 1H); 7.92 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); 7.22 (d, J = 8.8 Hz, 1H); 7.16-7.09 (m, 3H); 6.96 (t, J = 7.5 Hz, 1H); 6.76 (d, J = 7.9 Hz, 1H); 6.65-6.56 (m, 2H); 4.87 (s, 2H); 4.42 (d, J = 5.3 Hz, 2H); 3.44 (s, 3H); 3.26 (s, 3H).	33
321	462		CH	CH	N-(2-Amino-phenyl)-4-[(6-methyl-6H-indolo[2,3-b]quinoxalin-9-ylamino)-methyl]-benzamide	[1]**H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.60 (s, 1H); 8.19 (d, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 7.95 (d, J = 7.9 Hz, 2H); 7.76 (t, J = 7.0 Hz, 1H); 7.65 (t, J = 7.9 Hz, 1H); 7.57 (d, J = 7.9 Hz, 2H); 7.54 (d, J = 8.8 Hz, 1H); 7.41 (d, J = 1.3 Hz, 1H); 7.22 (dd, J = 1.8, 8.8 Hz, 1H); 7.14 (d, J = 7.9 Hz, 1H); 6.95 (t, J = 7.5 Hz, 1H); 6.76 (t, J = 7.9 Hz, 1H); 6.57 (t, J = 7.5 Hz, 1H); 6.51 (bs, 1H); 4.86 (bs, 2H); 4.54 (d, J = 4.8 Hz, 2H); 3.85 (s, 3H).	33

Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
322	463		N	CH	*N*-(2-Amino-phenyl)-6-(1-hydroxy-cyclohexylethynyl)-nicotinamide	LRMS calc: 335.40, found: 336.1 $(MH)^+$	14, 3
323	464		N	CH	*N*-(2-Amino-phenyl)-6-p-tolylsulfanyl-nicotinamide	LRMS calc: 335.42, found: 336.1 $(MH)^+$	14, 3
324	465		CH	CH	*N*-(2-Amino-phenyl)-4-[5-(indan-2-ylaminomethyl)-thiophen-2-ylmethyl]-benzamide	LRMS calc: 453.6, found: 454.2 $(MH)^+$	21
325	466		CH	CH	*N*-(2-Amino-phenyl)-4-[5-(pyridin-2-ylaminomethyl)-thiophen-2-ylmethyl]-benzamide	LRMS calc: 414.52, found: 415 $(MH)^+$	21
326	467		CH	CH	*N*-(2-Amino-phenyl)-4-[(5-bromo-thiazol-2-ylamino)-methyl]-benzamide	LRMS calc: 403.3, found: 404 $(MH)^+$	21

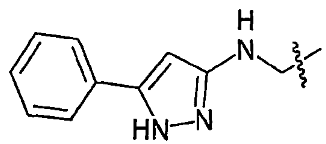
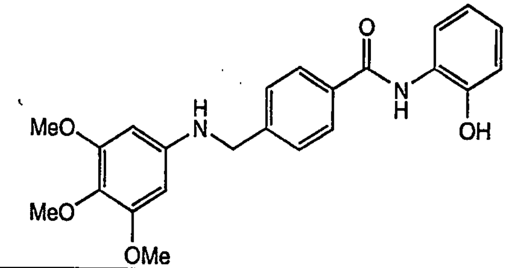
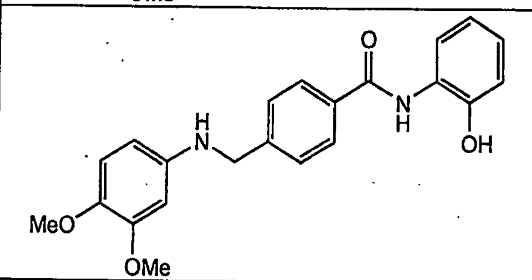
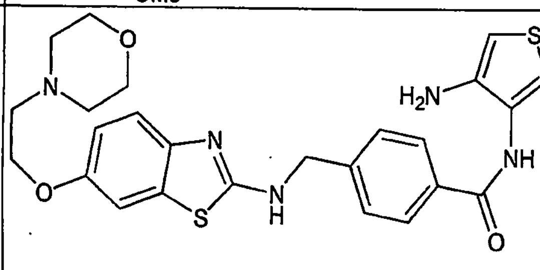
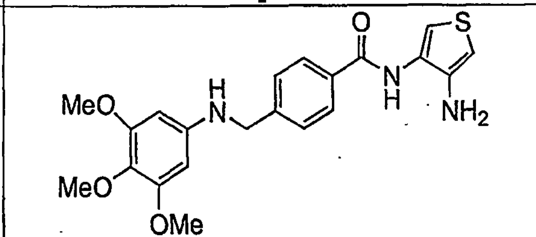
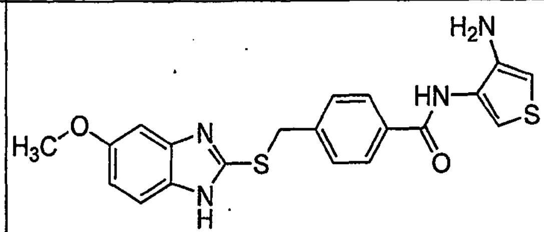
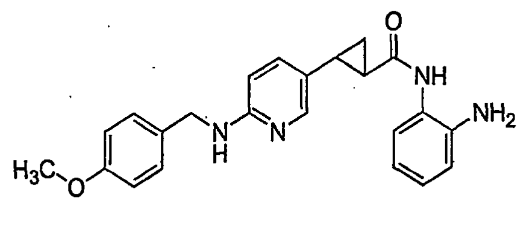
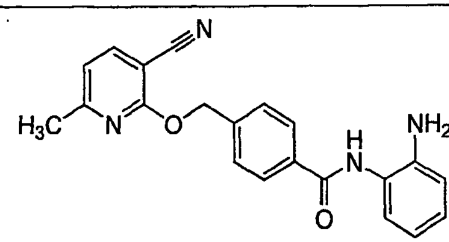
Ex.	Cpd	W	Y	Z	Name	Characterization	Schm
327	468		CH	CH	*N*-(2-Amino-phenyl)-4-[(5-phenyl-1H-pyrazol-3-ylamino)-methyl]-benzamide	LRMS calc: 483.45, found: 484.1 $(MH)^+$	21

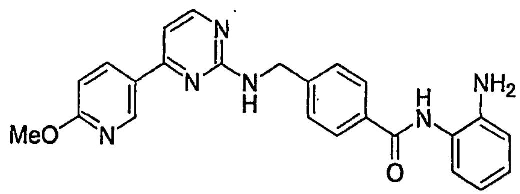
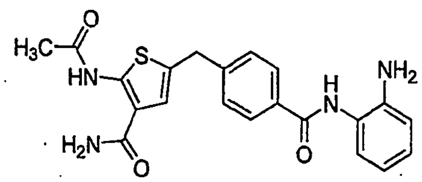
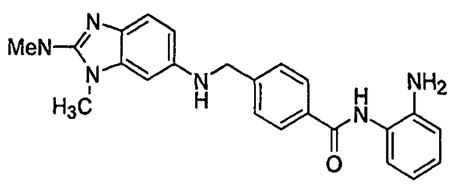
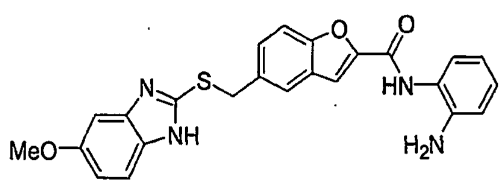
Table 4c

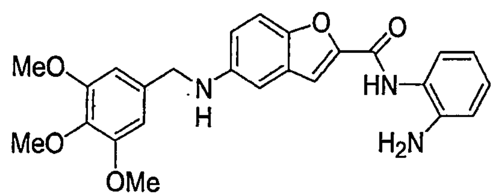
Characterization of Additional Compounds

Ex.	Cpd	Compound	Name	Characterization	Schm
426	571		*N*-(2-Hydroxy-phenyl)-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR (DMSO-d_6):** δ 9.57 (brs, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.07 (t, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 6.85 (t, *J* = 7.9 Hz, 1H), 6.21 (t, *J* = 6.1 Hz, 1H), 5.95 (s, 2H), 4.38 (d, *J* = 5.7 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H).	33, 55
427	572		*N*-(2-hydroxy-phenyl)-4-[(3,4-Dimethoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR (300 MHz, DMSO-D_6)** δ (ppm): 9.9 (bs, 1H), 9.53 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.96 (d, *J* = 7.9, Hz, 1H), 6.88 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.38 (s, 1H), 6.05 (m, 2H), 4.36 (d, *J* = 5.7 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).	33, 55
428	573		*N*-(4-Amino-thiophen-3-yl)-4-{[6-(2-morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide	**^{1}H NMR: (Acetone-d_6)** δ (ppm): 9.09 (bs, 1H), 8.03 (d, J=7.9Hz, 2H), 7.96 (d, J=7.5 Hz, 1H), 7.65 (d, J=7.9 Hz, 2H), 7.61 (d, J=3.5 Hz, 1H), 7.51 (bs, 2H), 7.41 (d, J=8.8 Hz, 1H), 7.36 (s, 1H), 6.95 (d, J=6.2 Hz, 1H), 6.35 (d, J=3.5 Hz, 1H), 4.85 (s, 2H), 4.20 (t, J=5.7 Hz, 2H), 3.69)t, J=4.4 Hz, 4H), 2.87-2.81(m, 2H), 2.62-2.57 (m, 4H).	33, 60

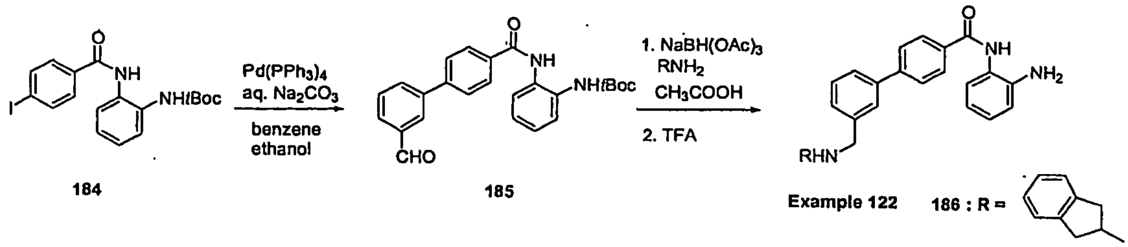
Ex.	Cpd	Compound	Name	Characterization	Schm
429	574		*N*-(4-Amino-thiophen-3-yl)-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR (DMSO-d$_6$):** δ 9.66 (brs, 1H), 7.94 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 6.22-6.16 (m, 1H), 5.94 (s, 2H), 4.91 (s, 2H), 4.38 (d, J = 5.7 Hz, 4H), 3.70 (s, 6H), 3.55 (s, 3H).	33, 60
430	575		*N*-(4-Amino-thiophen-3-yl)-4-(5-methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide	**(DMSO)** δ (ppm):12.43 (bs, 1H), 9.59 (bs, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 3.7 Hz, 1H), 7.32 (bs, 1H, SCH), 6.96 (bs, 1H, SCH), 6.74 (dd, J = 8.8, 2.2 Hz, 1H), 6.11(d, J = 3.7 Hz, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 3.76 (s, 3 H).LRMS: 410.1(calc) (M); 411.2(found)(M+H)+	36, 60
431	576		2-[4-(4-Methoxy-benzylamino)-phenyl]-cyclopropanecarboxylic acid (2-amino-phenyl)-amide	^{1}H-NMR (DMSO-d6), δ (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.63 (d, J=7.1 Hz, 1H), 7.53 (t, J= 4.2 Hz, 1H), 7.41 (dd, J=9.2, 1.5 Hz, 1H), 7.25 (d, J=8.3 Hz, 2H), 7.06 (d, J=7.1 Hz, 1H), 6.85 (d, J=8.3 Hz, 2H), 6.62-6.59 (m, 3H), 4.51 (d, J= 4.2 Hz, 2H), 3.78 (s, 3H), 2.77 (d, J=3.1 Hz, 1H), 2.45 (d, J=1.1 Hz, 1H), 1.22 (m, 1H), 1.05 (m, 1H).	
432	577		*N*-(2-Amino-phenyl)-4-(3-cyano-6-methyl-pyridin-2-yloxymethyl)-benzamide	**^{1}H NMR (DMSO-d$_6$) δ (ppm):** 9.72 (brs, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.5 hz, 1H), 5.62 (brs, 2H), 4.97 (brs, 2H)	11

SUBSTITUTE SHEET (RULE 26)

Ex.	Cpd	Compound	Name	Characterization	Schm
433	578		*N*-(2-Amino-phenyl)-4-{[4-(6-methoxy-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide	**^{1}H NMR (300 MHz, DMSO-D_6) δ (ppm):** 9.63 (s, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 5.3 Hz, 2H), 7.96 (m, 3H), 7.54 (d, J = 7.5Hz, 2H), 7.22 (dd, J = 5.3, 7.8 Hz, 2H), 7.01 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H), 6.64 (dd, J = 7.0, 7.9 Hz, 1H), 4.92 (s, 2H), 4.70 (d, J = 6.2 Hz, 2H), 3.98 (s, 3H).	15, 33
434	579		2-Acetylamino-5-[4-(2-amino-phenylcarbamoyl)-benzyl]-thiophene-3-carboxamide	**^{1}H NMR: (DMSO) δ (ppm):** 11.98 (bs, 1H), 9.61 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.81 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 4.88 (bs, 2H), 4.10 (s, 2H), 2.15 (s, 3H).	49
435	580		*N*-(2-Amino-phenyl)-4-[(3-methyl-2-methylamino-3H-benzoimidazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR (DMSO) δ (ppm):** 9.56 (s, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 13.2, 8.35 Hz, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.39 (s, 1H), 6.31 (m, 2H), 5.75 (t, J = 6.15 Hz, 1H), 4.87 (s, 2H), 4.32 (d, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.82 (d, J = 8.5 Hz, 3H).	61
438	591		5-(5-Methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)amide	**^{1}H NMR (DMSO) δ (ppm):** 9.84 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.78-6.74 (m, 3H), 6.59 (t, J = 7.5 Hz, 1H), 5.71 (s, 2H), 4.94 (s, 1H), 4.65 (s, 2H), 3.76 (s, 3H).	64

Ex.	Cpd	Compound	Name	Characterization	Schm
439	592		5-(3,4,5-Trimethoxy-benzylamino)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	^{1}H NMR (DMSO) δ(ppm): 9.69 (s, 1H), 7.47 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 6.6 Hz, 1H), 6.97 (dd, J = 7.5, 7.5 Hz, 1H), 6.89 (dd, J = 8.8, 2.2 Hz, 1H), 6.79-6.78 (m, 2H), 6.74 (s, 2H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H), 6.14 (t, J = 5.7 Hz, 1H), 4.92 (s, 2H), 4.21 (d, J = 5.7 Hz, 1H), 3.75 (s, 6H), 3.31 (s, 3H).	64

Scheme 21



Example 122

Step 1: {2-[(3'-Formyl-biphenyl-4-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester (185)

[0254] Following the procedure described in Example 15, step 1, but substituting 184 for 140, the title compound 185 was obtained in 74% yield. ^{1}H NMR ($CDCl_3$): δ 10.10 (s, 1H), 9.41(s, 1H), 8.13 (m, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.89 (m, 2H), 7.77 (m, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.64 (m, 1H), 7.27-7.09 (m, 3H), 7.03 (s, 1H), 1.52 (s, 9H).

Step 2: *N*-(2-Aminophenyl)-4-[3-(indan-2-ylaminomethyl)phenyl)]-benzamide (**186**)

[0255] To a stirred solution of biphenyl aldehyde (104 mg, 0.25 mmol) and 2-aminoindane (33.3 mg, 0.25 mmol) in dichloroethane (1mL) was added sodium triacetoxyborohydride (80 mg, 0.375 mmol) followed by a glacial acetic acid (15ul, 0.25 mmol), and then the mixture was stirred at room temperature for 3h. After a removal of the volatiles, the residue was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The combined organic layers were washed with water, dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired Boc-monoprotected product (112mg, 84% yield) as a white solid. ^{1}H NMR ($CDCl_3$): □□9.21 (s, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.83 (m, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.65 (s, 1H), 7.54-7.38 (m, 3H), 7.28 (m, 7H), 6.82 (s, 1H), 3.95 (s, 2H), 3.74 (m, 1H), 3.22 (dd, J = 15.6, 6.9 Hz, 2H), 2.89 (dd, J = 15.6, 6.6 Hz, 2H), 1.53 (s, 9H).

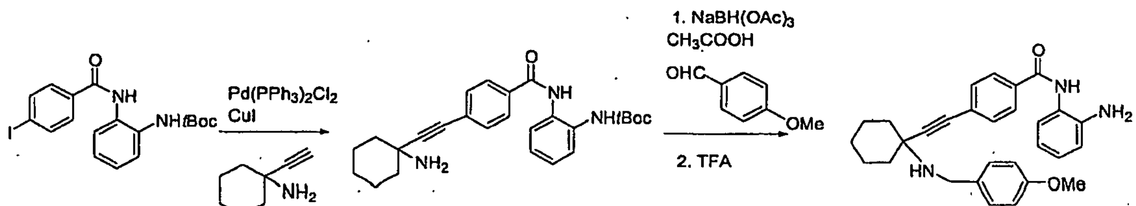
[0256] Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **186** was obtained in 98 % yield. ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.95 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.57 (m, 1H), 7.54-6.79 (m,

11H), 3.95 (s, 2H), 3.66 (m, 1H), 3.16 (dd, J = 15.6, 6.9 Hz, 2H), 2.81 (dd, J = 15.6, 6.6 Hz, 2H).

Examples 123-126

[0257] Examples 123 to 126 (compounds 187 - 190) were prepared using the same procedure as described for compound 186 in Example 122 (scheme 21).

Scheme 22



184 191 192

Example 127

Example 127

Step 1: {2-[4-(1-Amino-cyclohexylethynyl)-benzoylamino]-phenyl}-carbamic acid *tert*-butyl ester (191)

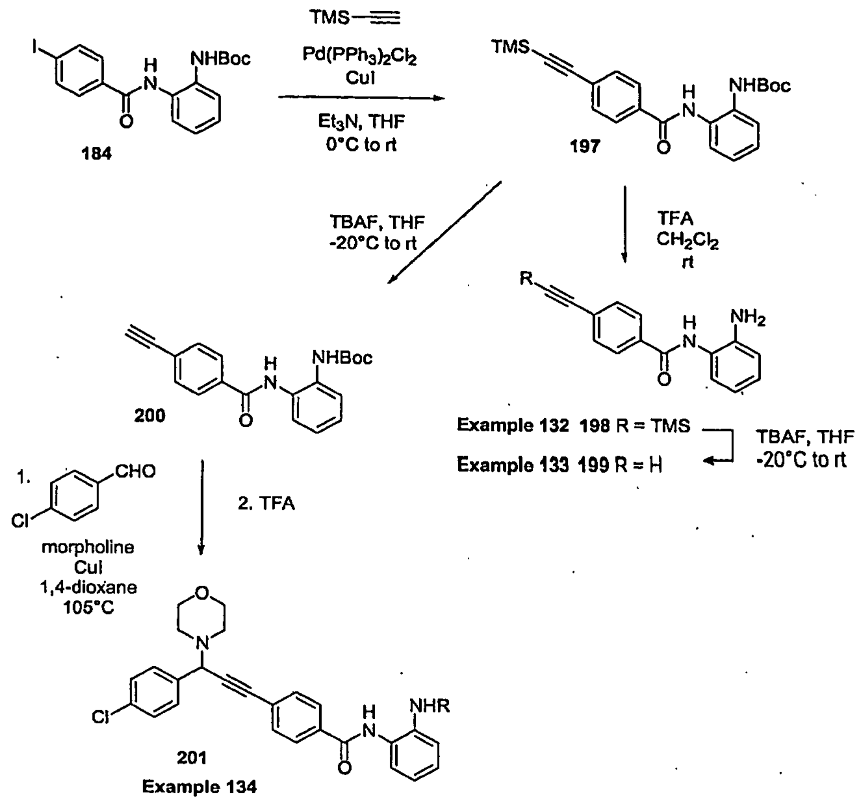
[0258] A mixture of iodide **184** (438 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), triphenylphosphine (7.6 mg, 0.025 mmol), and 1-ethynylcyclohexylamine (185 mg, 1.5 mmol) was stirred at room temperature in THF (4 mL) containing triethylamine (0.56 mL, 4.0 mmol) for 20 min. To this CuI (3.8 mg, 0.02 mmol) was added and stirring continued for 2 h. The reaction mixture was then diluted with ethyl acetate (30 mL), washed with water, and the organic layer was dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired product **191** (420 mg, 97% yield). ^{1}H NMR ($CDCl_3$): δ 9.36 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.25-6.85 (m, 3H), 2.10-1.30 (m. 10H), 1.51 (s, 9H).

Step 2: *N*-(2-Aminophenyl)-4-[1-(4-methoxy-benzylamino)-cyclohexylethynyl]-benzamide (192)

[0259] Following the procedure described in Example 122, step 2, but substituting *p*-anisaldehyde for 2-aminoindane, the title compound **192** was obtained in 74 % yield. ^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.31 (d, J

= 8.4 Hz, 2H), 7.23 (m, 1H), 7.05 (m,1H), 6.84 (d, J =8.7 Hz, 2H), 6.78 (m, 2H), 3.97 (s, 2H), 3.76 (s, 3H), 2.10-1.30 (m. 10H).

Scheme 23



Example 133

<u>Step 1: *N*-[2-(t-Butyloxycarbonyl)-amino-phenyl]-4-(trimethylsilylethynyl)benzamide (**197**)</u>

[0260] To a stirred solution of **184** (5.00 g, 11.41 mmol) in anhydrous THF (100 ml) under nitrogen at 0°C were added $Pd(PPh_3)_2Cl_2$ (240 mg, 0.34 mmol), CuI (130 mg, 0.69 mmol), and trimethylsilylacetylene (2.10 ml, 14.84 mmol), respectively. Then, anhydrous Et_3N (6.36 ml, 45.66 mmol) was added dropwise. The temperature was slowly warmed up to room temperature over 4 h. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with ethyl acetate. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 20/80→50/50) to afford the title compound **197** (4.42 g, 10.83 mmol, 94% yield) as a yellow powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.26 (bs, 1H), AB system (δ_A = 7.91, δ_B = 7.55, J = 8.3 Hz,

4H), 7.85 (d, J = 7.9 Hz, 1H), 7.32-7.13 (m, 3H), 6.70 (bs, 1H), 1.53 (s, 9H), 0.28 (s, 9H).

Step 2: *N*-(2-Amino-phenyl)-4-(trimethylsilylethynyl)benzamide (**198**)

[0261] Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **198** (70 mg, 0.23 mmol) was obtained as a white solid with a major fraction composed of a mixture of **198** and **199**. ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.20 (bs, 1H), AB system (δ_A = 8.07, δ_B = 7.62, J = 8.2 Hz, 4H), 7.32 (d, J = 7.6 Hz, 1H), 7.05 (td, J = 7.6, 1.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 4.66 (bs, 2H), 0.30 (s, 9H).

Step 3: *N*-(2-Amino-phenyl)-4-ethynylbenzamide (**199**)

[0262] To a stirred solution at −20°C of a mixture of **198** and **199** in anhydrous THF (15 ml) under nitrogen was added a solution of TBAF (1 ml, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 18 h. Then, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and diluted with ethyl acetate. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 30/70) to afford the title compound **199** (215 mg, 0.91 mmol, 46% yield over 2 steps) as a pale yellow powder. ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.19 (bs, 1H), AB system (δ_A = 8.08, δ_B = 7.66, J = 8.5 Hz, 4H), 7.33 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 4.67 (bs, 2H), 3.88 (s, 1H).

Example 134

Step 1: *N*-[2-(*t*-Butyloxycarbonyl)-amino-phenyl]-4-ethynylbenzamide (**200**)

[0263] To a stirred solution at −20°C of a mixture of **199** (3.48 g, 8.53 mmol) in anhydrous THF (50 ml) under nitrogen was slowly added a solution of TBAF (9.4 ml, 9.38 mmol, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 4 h. Then, the reaction mixture was concentrated, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was

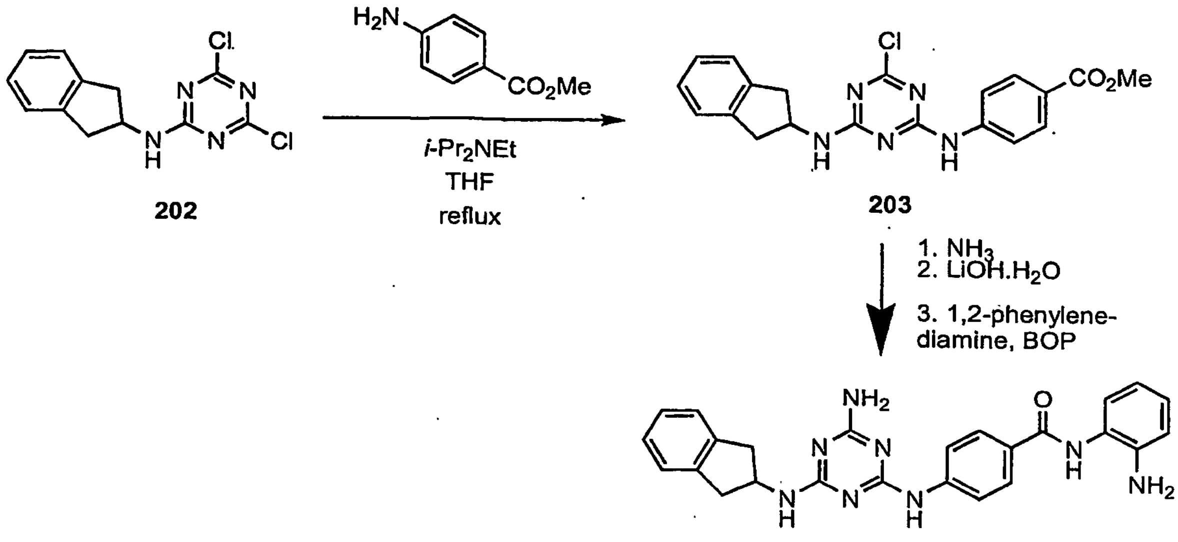
then purified by flash chromatography on silica gel (AcOEt/hexane: 25/75→30/70) to afford the title compound **200** (2.53 g, 7.53 mmol, 88% yield) as a pale yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.31 (bs, 1H), AB system (δ_A = 7.94, δ_B = 7.59, J = 8.5 Hz, 4H), 7.83 (d, J = 7.6 Hz, 1H), 7.30-7.10 (m, 3H), 6.75 (bs, 1H), 3.23 (s, 1H), 1.53 (s, 9H).

Step 2: *N*-(2-amino-phenyl)-4-[3-(4-chlorophenyl)-3-morpholin-4-yl-1-propyn-1-yl]-benzamide (**201**)

To a stirred solution at room temperature of **200** (200 mg, 0.60 mmol) in anhydrous 1,4-dioxane (5 ml) under nitrogen were added 4-chlorobenzaldehyde (100 mg, 0.71 mmol), morpholine (60 µl, 0.68 mmol), and CuI (6 mg, 0.03 mmol), respectively. The reaction mixture was bubbled with nitrogen for 5 min and warmed up to 105°C. After 18 h, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the desired compound (193 mg, 0.35 mmol, 59% yield) as a pale yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.40 (bs, 1H), AB system (δ_A = 7.96, δ_B = 7.36, J = 8.5 Hz, 4H), 7.79 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.4 Hz, 4H), 7.25-7.10 (m, 3H), 6.91 (s, 1H), 4.80 (s, 1H), 3.82-3.68 (m, 4H), 2.69-2.58 (m, 4H), 1.53 (s, 9H).

[0264] Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **201** was obtained in 67 % yield. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.80 (bs, 1H), AB system (δ_A = 8.06, δ_B = 7.71, J = 8.1 Hz, 4H), AB system (δ_A = 7.65, δ_B = 7.52, J = 8.3 Hz, 4H), 7.20 (d, J = 7.9 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 7.0 Hz, 1H), 6.64 (t, J = 7.5 Hz, 1H), 5.10 (s, 1H), 4.97 (bs, 2H), 3.72-3.58 (m, 4H), 2.67-2.46 (m, 4H).

Scheme 24



Example 135 **204**

Example 135

Step 1: Methyl 4-(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-benzoic ester (**203**)

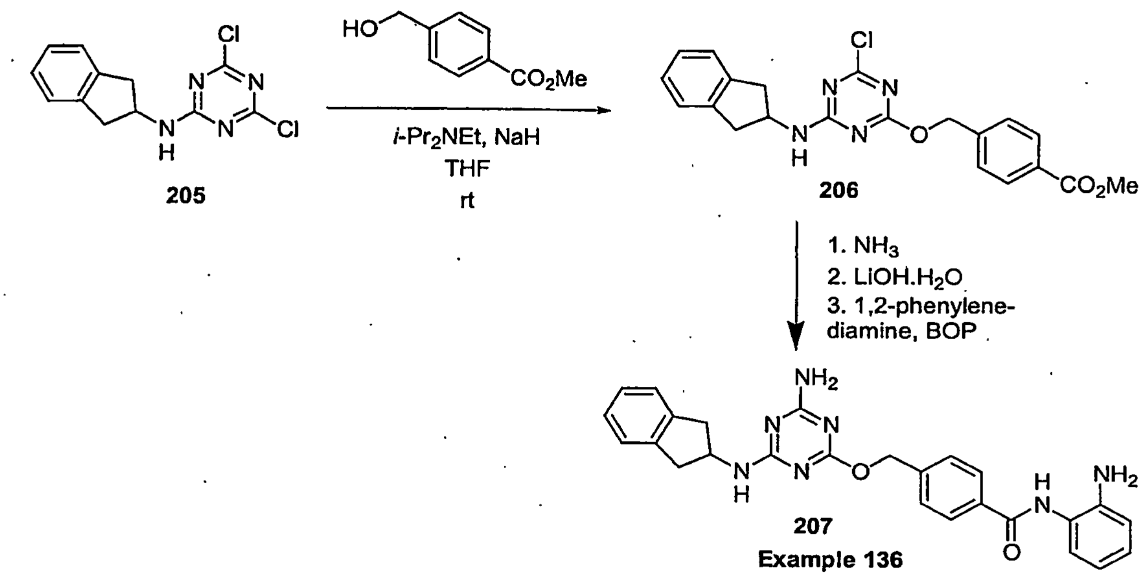
[0265] To a stirred solution at room temperature of **202** (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added *i*-Pr_2NEt (1.86 ml, 10.66 mmol) and methyl 4-aminobenzoate (1.29 g, 8.53 mmol) or $ArNH_2$ (1.2 equiv), respectively. The reaction mixture was then refluxed for 24 h. After cooling, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat*. NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($AcOEt/CH_2Cl_2$: 2/98→5/95) to afford the title compound **203** (1.70 g, 4.30 mmol, 60% yield) as a beige powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): mixture of rotamers, 2 AB system (δ_A = 8.03, $\delta_{A'}$ = 8.00, δ_B = 7.70, $\delta_{B'}$ = 7.61, $J_{AB} = J_{A'B'}$ = 8.8 Hz, 4H), 7.43 and 7.31 (2 bs, 1H), 7.29-7.19 (m, 4H), 5.84 and 5.78 (2 d, J = 7.2 and 7.7 Hz, 1H), 4.98-4.77 (2 m, 1H), 3.91 and 3.90 (2 s, 3H), 3.41 (dd, J = 16.1, 7.0 Hz, 2H), 2.94 and 2.89 (2 dd, J = 15.9, 4.9 Hz, 2H).

Step 2: 4-[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-*N*-(2-amino-phenyl)-benzamide (**204**)

[0266] The title compound **204** was obtained from **203** in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. ^1H

NMR (300 MHz, acetone-d_6) δ (ppm): mixture of rotamers, 8.98 (m,1H), 8.49 and 8.28 (2m, 1H), 8.10-7.92 (m, 4H), 7.35-7.14 (m, 5H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 6.6, 1.3 Hz, 1H), 6.71 (td, J = 7.6, 1.3 Hz, 1H), 6.57 and 6.42 (2m, 1H), 6.04 and 5.86 (2m, 2H), 4.92-4.76 (m, 1H), 4.70-4.58 (m, 1H), 3.44-3.26 (m, 2H), 3.08-2.92 (m, 2H). HRMS (calc.): 452.2073, (found): 452.2062.

Scheme 25



Example 136

<u>Step 1: Methyl 4-[(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yloxy)-methyl]-benzoic ester (**206**)</u>

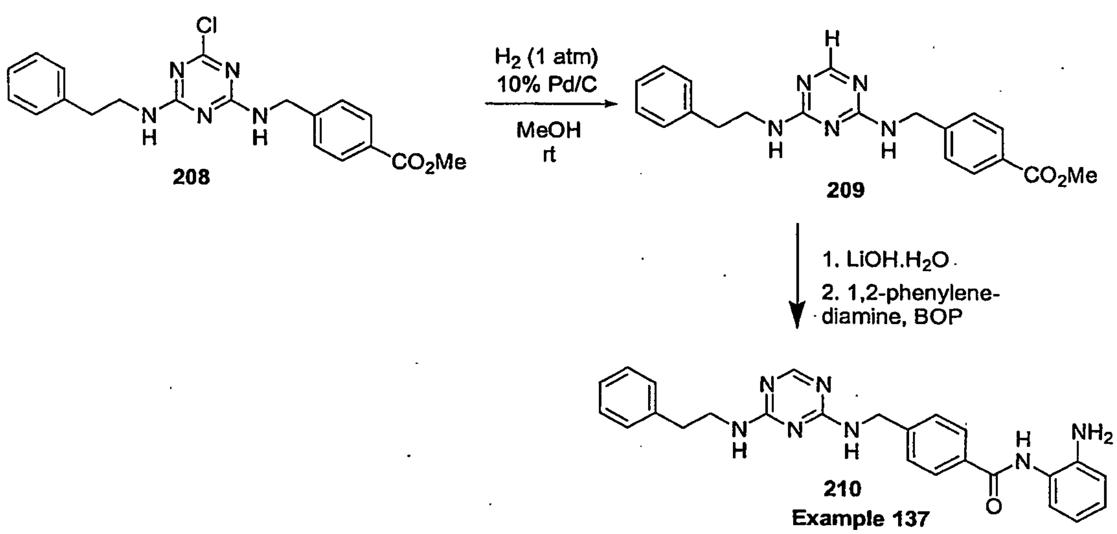
[0267] To a stirred solution at 0°C of **205** (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added *i*-Pr_2NEt (1.86 ml, 10.66 mmol) and methyl 4-(hydroxymethyl)benzoate (1.30 g, 7.82 mmol). After few minutes, NaH (95%, 186 mg, 7.11 mmol) was added portionwise. Then, the reaction mixture was allowed to warm to room temperature. After 24 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($AcOEt/CH_2Cl_2$: 2/98) to afford the title compound **206** (2.00 g, 4.88 mmol, 69% yield) as a colorless sticky foam. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): mixture of rotamers, 2 AB system (δ_A = 8.06, $\delta_{A'}$ = 8.03, δ_B = 7.52, $\delta_{B'}$ = 7.46, J_{AB} = $J_{A'B'}$ = 8.5

Hz, 4H), 7.26-7.17 (m, 4H), 5.94 and 5.85 (2 bd, J = 7.8 Hz, 1H), 5.48 and 5.39 (2 s, 2H), 4.92-4.76 (2 m, 1H), 3.94 and 3.92 (2 s, 3H), 3.39 and 3.33 (2 dd, J = 16.0, 7.0 Hz, 2H), 2.89 and 2.84 (2 dd, J = 16.0, 4.9 Hz, 2H).

Step 2: 4-{[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yloxy]-methyl}-*N*-(2-amino-phenyl)-benzamide (207)

[0268] The title compound **207** was obtained from **206** in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. ^{1}H NMR (300 MHz, acetone-d_6 + ε DMSO-d_6) δ (ppm): 9.49 (m, 1H), 8.12-8.03 (m, 2H), 7.60 (t, J = 7.7 Hz, 2H), 7.35 (d, J =7.1 Hz, 1H), 7.28-7.13 (m, 4H), 7.07-6.94 (m, 2H), 6.90 (dd, J = 7.3, 1.4 Hz, 1H), 6.70 (td, J = 7.3, 1.1 Hz, 1H), 6.44 (bs, 1H), 6.25 (bs, 1H), 5.47 and 5.41 (2s, 2H), 4.87-4.68 (m, 3H), 3.35-3.20 (m, 2H), 3.02-2.88 (m, 2H). HRMS (calc.): 467.2070, (found): 467.2063.

Scheme 26



Example 210

Methyl 4-[(4-chloro-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (208)

[0269] The title compound **208** was obtained from **2** following the same procedure as in Example 1, pathway B steps 2 (R^1R^2NH = phenethylamine).

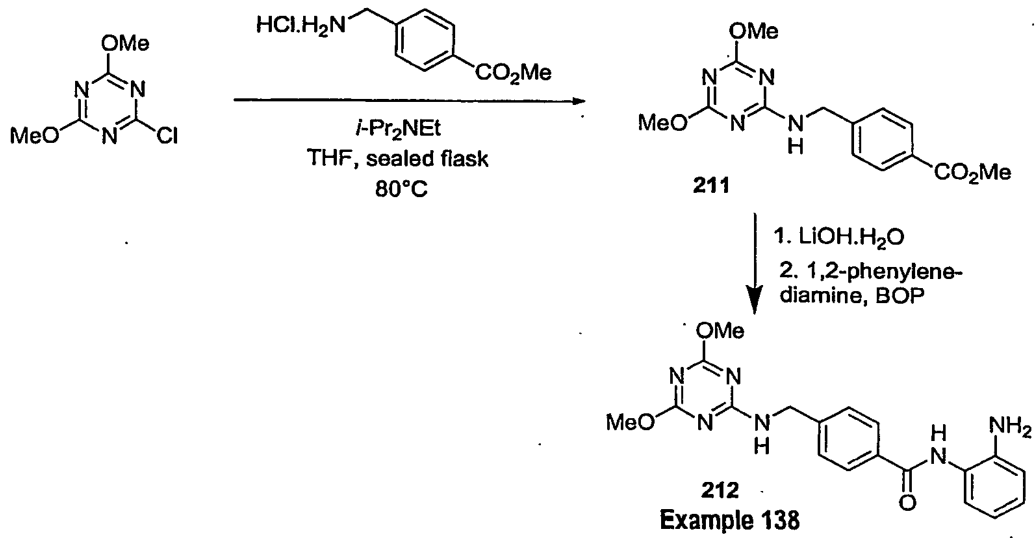
Step 1: Methyl 4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (209)

[0270] To a degazed solution of **208** (300 mg, 0.75 mmol) in MeOH (35 mL) was added 10% Pd/C (24 mg, 0.023 mmol). The reaction mixture was stirred under a 1 atm pressure of H_2 at room temperature for 20 h then it was purged with N_2. The palladium was removed by filtration through celite and the reaction mixture was concentrated. The crude residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 4/96) to afford the title compound **209** (135 mg, 0.37 mmol, 50% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.50-7.15 (m, 6H), 4.85-4.65 (m, 2H), 3.98 (s, 3H), 3.82-3.62 (m, 2H), 3.05-2.85 (m, 2H).

Step 2: *N*-(2-Amino-phenyl)-4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide (210)

[0271] The title compound **210** was obtained from **209** in 2 steps following the same procedure as in Example 1, steps 4 and 5. ^1H NMR: (300 MHz, acetone-d_6) δ (ppm): 9.03 (s, 1H), 8.17-7.87 (m, 3H), 7.49 (dd, J = 19.2, 8.2 Hz, 2H), 7.32-7.03 (m, 6H), 6.99 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-6.30 (m, 2H), 4.72 (t, J = 6.3 Hz, 1H), 4.65-4.56 (m, 1H), 3.67-3.51 (m, 2H), 2.95-2.80 (m, 2H).

Scheme 27



Example 138

Step 1: Methyl 4-[(4,6-dimethoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (211)

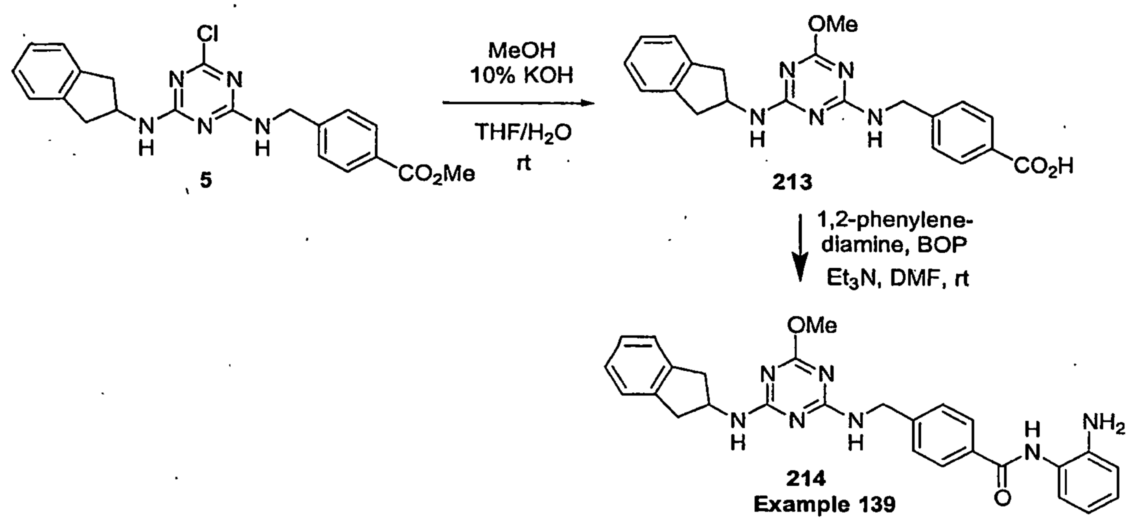
[0272] In a 75ml sealed flask, a stirred suspension of 2-chloro-4,6-dimethoxy-1,3,5-triazine (540 mg, 3.08 mmol), methyl 4-(aminomethyl)benzoate.HCl **2** (689 mg, 3.42 mmol), *i*-Pr_2NEt (1.49 ml, 8.54 mmol) in anhydrous THF (30 ml) was warmed at 80°C for 5 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 10/90→30/70) to afford the title compound **211** (870 mg, 2.86 mmol, 93% yield) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): AB system (δ_A = 8.01, δ_B = 7.39, J_{AB} = 8.5 Hz, 4H), 6.08-6.00 (m, 1H), 4.73 (d, J = 6.3 Hz, 2H), 3.95 (s, 6H), 3.92 (s, 3H).

[0273] The title compound **212** was obtained from **211** in 2 steps following the same procedure as Example 1, steps 4 and 5. ^1H NMR (300 MHz, acetone-d_6 + Σ DMSO-d_6) δ (ppm): 9.58 (bs, 1H), 8.27 (t, J = 6.3 Hz, 1H), AB system (δ_A = 8.04, δ_B = 7.53, J_{AB} = 8.4 Hz, 4H), 7.31 (d, J = 6.9 Hz, 1H),), 7.02 (td, J =7.6, 1.6 Hz, 1H), 6.88 (dd, J = 7.9, 1.4 Hz, 1H), 6.68 (td, J = 7.6, 1.4 Hz, 1H), 4.86-4.78

(m, 2H), 4.69 (d, J = 6.3 Hz, 2H),), 3.90 and 3.89 (2s, 6H). HRMS (calc.): 380.1597, (found): 380.1601.

Step 2: *N*-(2-Amino-phenyl)-4-[(4,6-dimethoxy-[1,3,5]-triazin-2-yl-amino)-methyl]-benzamide (212)

Scheme 28



Example 139

Step 1: 4-[(6-(2-Indanyl-amino)-4-methoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (213)

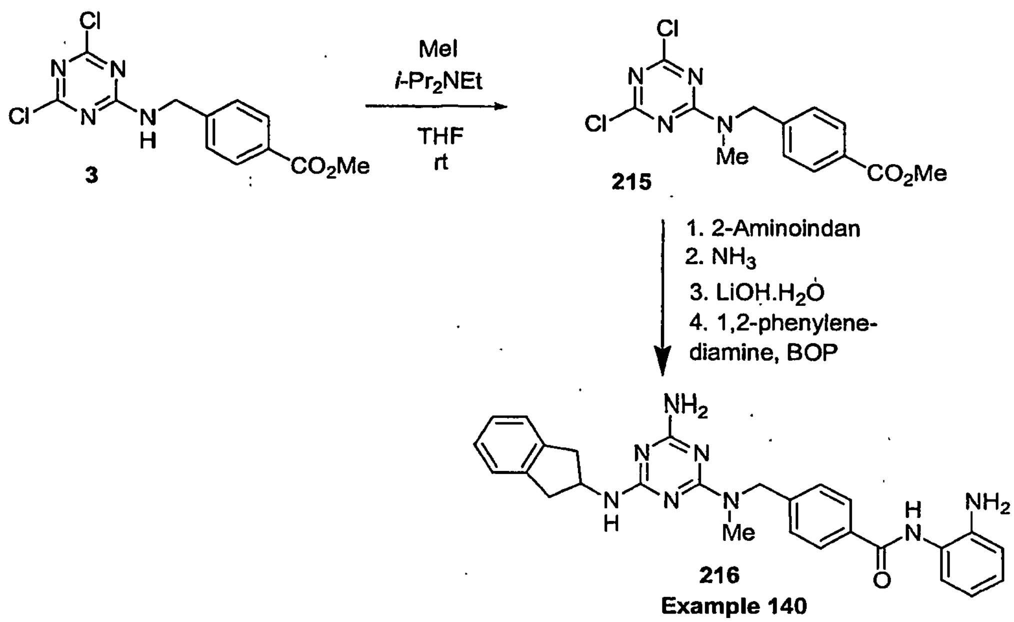
[0274] To a stirred solution at room temperature of **5** (300 mg, 0.73 mmol) in a mixture of MeOH/THF (10 ml/5 ml) was added an aqueous solution of KOH (10%, 5 ml). After 3 days, the reaction mixture was concentrated on the rotavap, diluted in water and acidified with 1N HCl until pH 5-6 in order to get a white precipitate. After 15 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **213** (282 mg, 0.72 mmol, 98% yield) as a white solid. MS: m/z = 392.1 $[MH]^{\cdot+}$.

Step 2: *N*-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-methoxy-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide (214)

[0275] The title compound **214** was obtained from **213** in one step following the same procedure as Example 1, step 5. ^{1}H NMR (300 MHz, acetone-d_6 + ϵ DMSO-d_6) δ (ppm): mixture of rotamers, 9.69-9.53 (m, 1H), AB system (δ_A = 8.04, δ_B = 7.52, J_{AB} = 7.8 Hz, 4H), 7.80-7.60 (m, 1H), 7.45-7.10 (m, 6H), 7.01 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 4.92-4.60 (m, 5H), 3.90-3.78 (m,

3H), 3.35-3.22 (m, 2H), 3.02-2.83 (m, 2H). HRMS (calc.): 481.2226, (found): 481.2231.

Scheme 29



Example 29

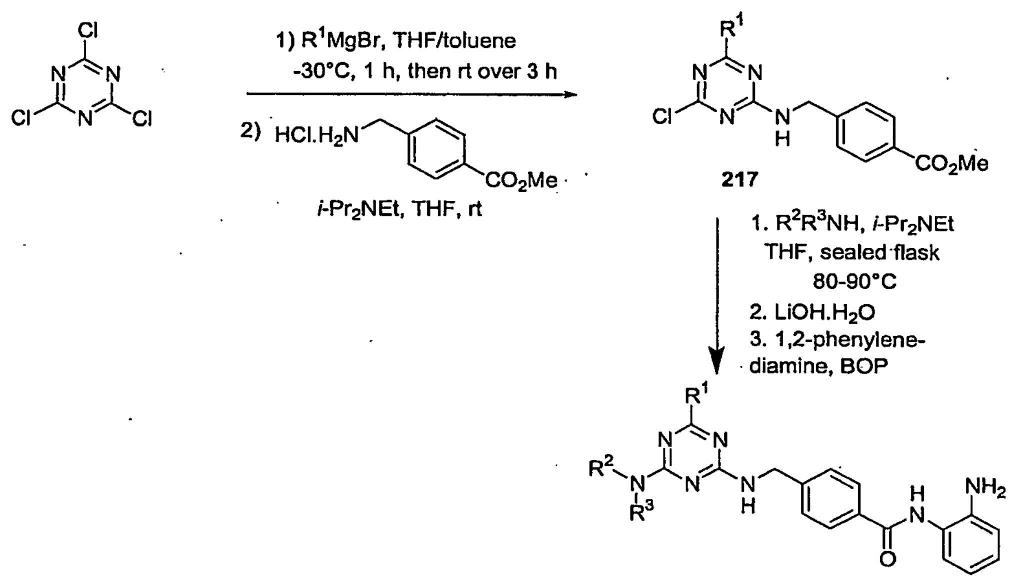
Step 1: Methyl 4-[(4,6-dichloro-[1,3,5]triazin-2-yl-*N*-methyl-amino)-methyl]-benzoic ester (**216**)

[0276] To a stirred suspension at room temperature of NaH (95%, 81 mg, 3.19 mmol) in anhydrous THF (10 ml) under nitrogen were successively added a solution of **3** (500 mg, 1.60 mmol) in anhydrous THF (10 ml) and MeI (298 µl, 4.79 mmol). After 16 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 10/90→20/80) to afford the title compound **215** (200 mg, 0.61 mmol, 38% yield) as a white crystalline solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): AB system (δ_A = 8.04, δ_B = 7.31, J_{AB} = 8.2 Hz, 4H), 4.93 (s, 2H), 3.93 (s, 3H), 3.18 (s, 3H).

Step 2: 4-{[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-*N*-methyl-amino]-methyl}-*N*-(2-amino-phenyl)-benzamide (**216**)

[0277] The title compound **216** from **215** in 4 steps was obtained following the same procedure as Example 1, Pathway B steps 2-5. ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 9.11 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.43 (bs, 2H), 7.33 (d, J = 7.7 Hz, 1H),), 7.28-7.09 (m, 4H), 7.04 (td, J =7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.5, 1.3 Hz, 1H), 6.25-6.05 (m, 1H), 5.82 and 5.64 (2bs, 2H), 5.00-4.56 (m, 5H), 3.42-2.76 (m, 7H). HRMS (calc.): 480.2386, (found): 480.2377.

Scheme 30



Example 141 218 :R^1 = Me, R^2R^3N = 2-indanyl-amino

Example 141:

Step 1: Methyl 4-[(4-chloro-6-methyl-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (**217**)

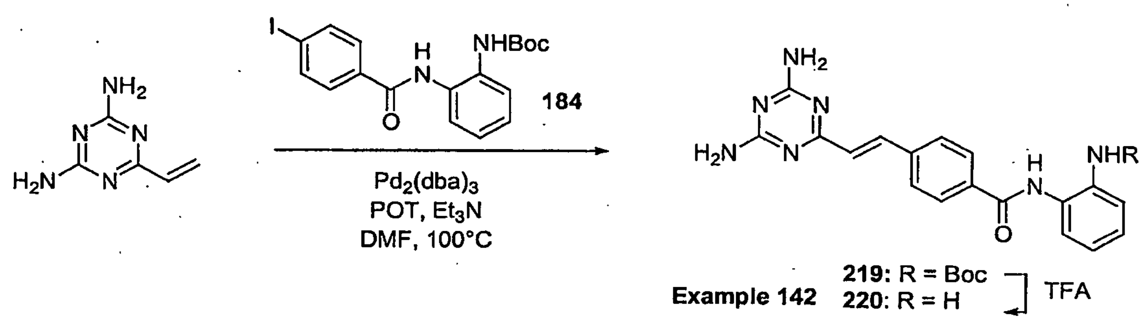
[0278] To a stirred solution at −30°C of cyanuric chloride **1** (2.00 g, 10.85 mmol) in anhydrous THF (100 ml) under nitrogen was slowly added a solution of MeMgBr (17 ml, 23.86 mmol, 1.4 M in anhydrous THF/toluene). After 1 h, the reaction mixture was allowed to warm to room temperature over 3 h. Then, methyl 4-(aminomethyl)benzoate.HCl **2** (2.08 g, 10.30 mmol) and *i*-Pr_2NEt (3.78 ml, 21.69 mmol) were added, respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was

successively washed with *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($AcOEt/CH_2Cl_2$: 10/90→15/85) to afford the title compound **217** (780 mg, 2.67 mmol, 25% yield) as a yellow powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): mixture of rotamers, 2 AB system (δ_A = 8.03, $\delta_{A'}$ = 8.02, δ_B = 7.39, $\delta_{B'}$ = 7.38, J = 8.5 Hz, 4H), 6.28-6.08 (2 m, 1H), 4.76 and 4.74 (2d, J = 6.3 Hz, 2H), 3.92 (s, 3H), 2.46 and 2.42 (2s, 3H).

Step 2: *N*-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-methyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide (**218**)

[0279] The title compound **218** was obtained from **217** in 3 steps following the same procedure as Example 1, steps 3-5. ^1H NMR (300 MHz, acetone-d_6 + Σ DMSO-d_6) δ (ppm): mixture of rotamers, 9.62-9.50 (m, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.68-7.37 (m, 3H), 7.33 (d, J = 7.7 Hz, 1H), 7.28-7.07 (m, 5H), 7.02 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 4.92-4.60 (m, 5H), 3.35-3.10 (m, 2H), 3.02-2.82 (m, 2H), 2.25-2.12 (m, 3H).

Scheme 31



Example 142

Step 1: (2-{4-[2-(4,6-Diamino-[1,3,5]triazin-2-yl)-vinyl]-benzoylamino}-phenyl)-carbamic tert-butyl ester (**219**)

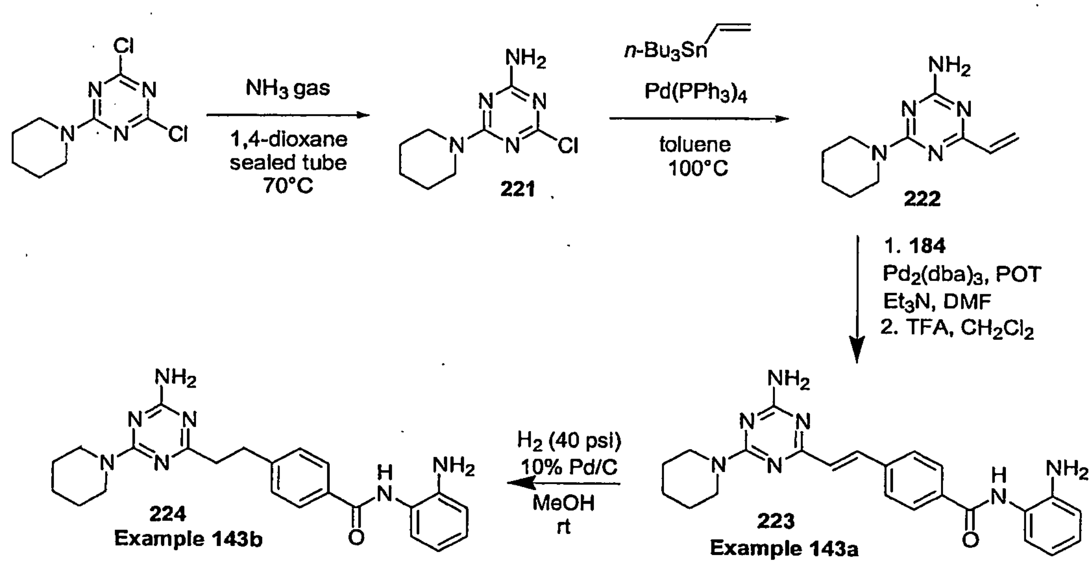
[0280] To a degazed solution of **184** (40 mg, 0.091 mmol) and 2-vinyl-4,6-diamino-1,3,5-triazine (11 mg, 0.083 mmol) in dry DMF (1 mL) was added tri-*o*-tolylphosphine (POT) (1.5 mg, 0.005 mmol) followed by Et_3N (46 μL, 0.33 mmol) and tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.0025 mmol). The solution was heated at 100°C for 16h. Then, DMF was removed under reduced pressure. The reaction mixture was partitioned between AcOEt and a solution of *sat.* NH_4Cl. After separation, the organic

layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 5/95) to afford the title compound **219** (25 mg, 0.056 mmol, 67% yield). ^1H NMR (300 MHz, Acetone-d_6) δ (ppm): 8.27 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 15.9 Hz, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.76-7.69 (m, 1H), 7.62-7.55 (m, 1H), 7.26-7.15 (m, 2H), 6.90 (d, J = 15.9 Hz), 6.21 (s, 4H), 1.50 (s, 9H).

Step 2: *N*-(2-Amino-phenyl)-4-[2-(4,6-diamino-[1,3,5]triazin-2-yl)-vinyl]-benzamide (**220**)

[0281] To a stirred solution at room temperature of **219** (25 mg, 0.056 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (0.3 mL, 4.3 mmol). After 30 min, a solution of sat. $NaHCO_3$ was slowly added until pH 8 is reached, CH_2Cl_2 was removed under reduced pressure, AcOEt was added, and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 10/90) to afford the title compound **220** (19 mg, 0.054 mmol, 98% yield). ^1H NMR: (300 MHz, acetone-d_6) δ (ppm): 8.33, 8.13 (2d, J = 7.5 Hz, 1H), 8.22 (d, J = 15.9 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.38-6.96 (m, 2H), 7.03 (d, J = 15.9 Hz, 1H), 6.94-6.62 (m, 2H).

Scheme 32



SUBSTITUTE SHEET (RULE 26)

Example 143a

Step 1: 2-Amino-4-chloro-6-piperidin-1-yl-[1,3,5]triazin (221)

[0282] Ammonia was bubbled for 5 min in a solution of 2,4-dichloro-6-piperidin-1-yl-[1,3,5]triazine (500 mg, 2.15 mmol) in dry 1,4-dioxane (20 mL). The solution was heated at 70°C for 16h in a sealed tube. The reaction mixture was allowed to cool to room temperature, and partitioned between AcOEt and a solution of *sat.* NH_4Cl. After separation, the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compound **221** (453 mg, 2.12 mmol, 98% yield). LRMS: $[MH]^{+} = 214.1$.

Step 2: 2-Amino 4-piperidin-1-yl-6-vinyl-[1,3,5]triazin **(222)**

[0283] To a solution of **221** (358 mg, 1.68 mmol) in dry toluene (7 mL) was added tributyl(vinyl)tin (514 µL, 1.76 mmol) followed by $Pd(PPh_3)_4$ (97 mg, 0.084 mmol) and the reaction mixture was heated at 100°C for 16h in a sealed tube. Then, the reaction mixture was allowed to cool to room temperature, concentrated, and purified directly by flash chromatography on silica gel (AcOEt/hexane: 10/90→30/70) to afford the title compound **222** (containing tributyltin chloride).

Steps 3: *N*-(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-vinyl]-benzamide (223)

[0284] The title compound **223** was obtained from **222** in 2 steps following the same procedure as in scheme 31, steps 1 and 2. ^1H NMR: (300 MHz, DMSO-d_6) δ (ppm): 9.69 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 16.0 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.04-6.92 (m, 1H), 6.91 (d, J = 16 Hz, 1H), 6.85-6.68 (m, 3H), 6.60 (t, J = 7.2 Hz, 1H), 4.93 (s, 2H), 3.77 (s, 4H), 1.63 (s, 2H), 1.52 (s, 4H).

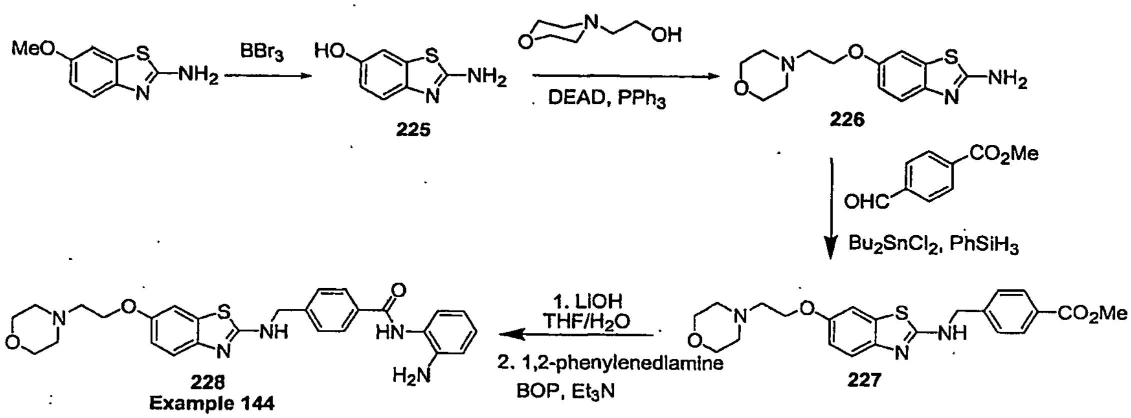
Example 143b

Step 4: *N*-(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-ethyl]-benzamide (**224**)

[0285] To a solution of **223** (18 mg, 0.043 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 0.021 mmol). The reaction mixture was shaked under a pressure of H_2 (40 psi) at room temperature for 16 h using an hydrogenation apparatus. Then, the reaction mixture was purged with N_2, filtered through celite, and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$:

2/98→4/96) to afford the title compound **224** (10 mg, 0.024 mmol, 56% yield). ^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD) δ (ppm): 7.82 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 7.0 Hz, 1H), 6.89-6.79 (m, 2H), 7.80-6.90 (m, 1H), 3.76 (s, 4H), 3.13 (t, J = 8.1 Hz, 2H), 2.88 (t, J = 8.1 Hz, 2H),1.90-1.40 (m, 10H).

Scheme 33



Example 144

Step 1: 2-Amino-benzothiazol-6-ol (225):

[0286] A suspension of 2-amino-6-methoxybenzothiazole (5.00 g, 27.8 mmol) in dichloromethane (70 mL) was cooled to 0°C under nitrogen and boron tribromide (3.93 mL, 41.6 mmol) was added dropwise. The light yellow mixture was stirred for 3 h, allowing to warm-up slowly from 0°C to 10°C. The reaction was slowly quenched by dropwise addition of methanol and tafter stirring overnight at room temperature, the white solid was collected by filtration (6.04 g, 88% yield). This hydrobromic salt was dissolved in water, washed with ethyl acetate, and neutralized with a saturated aqueous solution of $NaHCO_3$. The resulting crystals were collected by filtration and dried in the oven at 135°C for 1h to afford the title compound **225** as colorless crystals (3.63 g, 79% yield). ^{1}H NMR: (CD_3OD) δ (ppm): 7.27 (d, J=8.8 Hz, 1H), 7.08 (d, J=2.2 Hz, 1H), 6.80 (dd, J=8.4, 2.2 Hz, 1H).

Step 2: 6-(2-Morpholin-4-yl-ethoxy)-benzothiazol-2-ylamine (226)

[0287] To a solution of benzothiazole **225** (3.62 g, 21.8 mmol) in THF at room temperature under nitrogen, were successively added 4-(2-hydroxyethyl)morpholine (3.17 mL, 26.1 mmol), triphenylphosphine (7.43 g, 28.3 mmol) followed by a dropwise addition of diethyl

azodicarboxylate (4.46 mL, 28.3 mmol). The solution was stirred for 3.5 h and THF was partially removed *in vacuo*. The mixture was partitioned between ethyl acetate and H_2O. The combined organic layers were extracted with 1N HCl. The combined acidic extracts were neutralized using a saturated aqueous solution of $NaHCO_3$ and the precipitate was dissolved with ethyl acetate. These combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The filtrate was concentrated to afford the title compound **226** (5.83 g, 96% yield) as a light yellow oil. ^{1}H NMR: (Acetone-d_6) δ (ppm): 7.37 (d, J=8.8 Hz, 1H), 7.34 (d, J=2.6 Hz, 1H), 6.94 (dd, J=8.8, 2.6 Hz, 1H), 6.60 (bs, 2H), 4.19 (t, J=6.2 Hz, 2H), 3.70-3.67 (m, 4H), 2.90 (s, 2H), 2.81 (t, J=6.2 Hz, 2H), 2.62-2.58 (m, 4H).

Step 3: 4-{[6-(2-Morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzoic acid methyl ester (227):

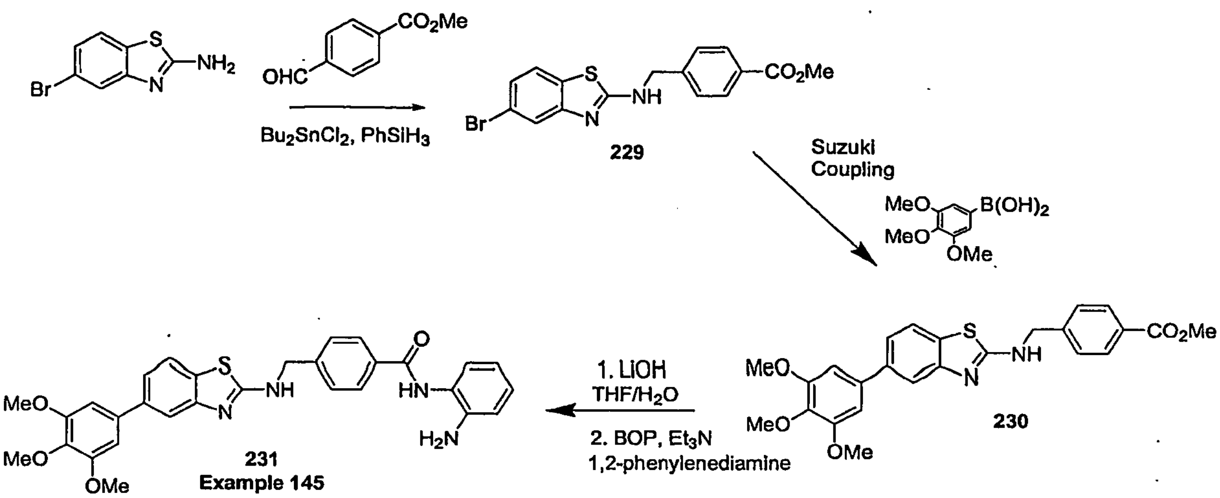
[0288] To a round-bottom flask containing benzothiazole **226** (5.80 g, 20.8 mmol) was added methyl 4-formylbenzoate (5.11 g, 31.1 mmol), followed by THF (8 mL), dibutyltin dichloride (315 mg, 1.04 mmol) and dropwise addition of phenylsilane (3.24 mL, 31.1 mmol). The resulting mixture was stirred overnight at room temperature under nitrogen. The mixture was diluted in ethyl acetate and filtered. The filtrate was partitioned between ethyl acetate and water and the combined organic layers were washed with 1N HCl. The combined acidic layers were neutralized using a saturated aqueous solution of $NaHCO_3$ and the precipitate was extracted with ethyl aceate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The resulting crude was purified by flash chromatography using MeOH/$CHCl_3$ (10:90) to afford **227** (3.69 g, 42% yield). ^{1}H NMR: (Acetone-d_6) δ (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J= 8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J= 8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H).

Step 4: *N*-(2-Amino-phenyl)-4-{[6-(2-morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (228):

[0289] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **228** was obtained (958 mg, 46%) as a colorless solid. ^{1}H NMR: (CD_3OD) δ (ppm): 8.04 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.40 (d, J=8.8 Hz, 1H), 7.31 (d, J=2.5 Hz, 1H), 7.25 (d, J=7.4 Hz, 1H), 7.15

(t, J=7.4 Hz, 1H), 6.97 (dd, J=8.8, 2.5 Hz, 2H), 6.84 (t, J=7.4 Hz, 1H), 4.78 (s, 2H), 4.21 (t, J=5.2 Hz, 2H), 3.81-3.77 (m, 4H), 2.87 (t, J=5.5, 2H), 2.69-3.66 (m, 4H).

Scheme 34



Example 145

Step 1: 4-[(5-Bromo-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (229):

[0290] Following the procedure described in Example 144, step 3, but substituting the 2-amino-6-bromobenzothiazole for **226**, the title compound **229** was obtained in 56% yield. ^{1}H NMR: (DMSO-d_6) δ (ppm): 8.78 (t, J= 5.9 Hz, 1H), 8.01 (d, J= 8.2 Hz, 2H), 7.99 (s, 1H), 7.56 (d, J= 8.2 Hz, 2H), 7.43-7.34 (m, 2H), 4.74 (d, J= 5.9 Hz, 2H), 3.90 (s, 3H).

Step 2: 4-{[5-(3,4,5-Trimethoxy-phenyl)-benzothiazol-2-ylamino]-methyl}-benzoic acid methyl ester (230):

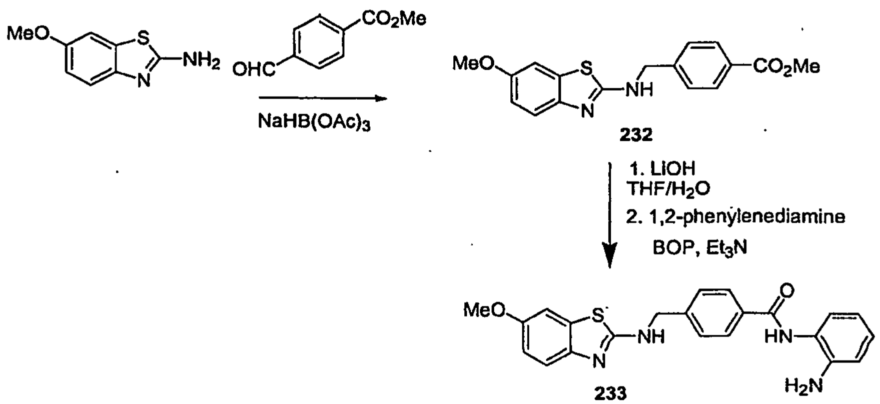
[0291] Following the procedure described in Example 15, step 1, but substituting **229** for **140**, the title compound **230** was obtained in 44%yield as colorless crystals. ^{1}H NMR: (DMSO-d_6) δ (ppm): 8.73 (t, J=5.7 Hz, 1H), 8.11 (d, J=1.8 Hz, 1H), 8.02 (d, J=8.4 Hz, 2H), 7.63-7.57 (m, 3H), 7.48 (d, J=8.4 Hz, 1H), 6.97 (s, 2H), 4.77 (d, J=5.7 Hz, 2H), 3.92 (m, 6H), 3.90 (s, 3H), 3.74 (s, 3H).

Step 3: *N*-(2-Amino-phenyl)-4-{[5-(3,4,5-trimethoxy-phenyl)-benzothiazol-2-ylamino]-methyl}-benzamide (231):

[0292] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound 231

was obtained in 69% yield. ^{1}H NMR: (Acetone-d_6) δ (ppm): 8.31 (d, J=7.9 Hz, 2H), 8.20 (d, J=7.5 Hz, 1H), 8.13 (s, 1H), 7.73-7.58 (m, 3H), 7.63 (d, J=7.5 Hz, 2H), 7.48-7.43 (m, 2H), 7.05 (s, 2H), 4.98 (s, 2H), 4.00 (s, 6H), 3.84 (s, 3H).

Scheme 35



Example 146

Step 1: 4-[(6-Methoxy-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (**232**):

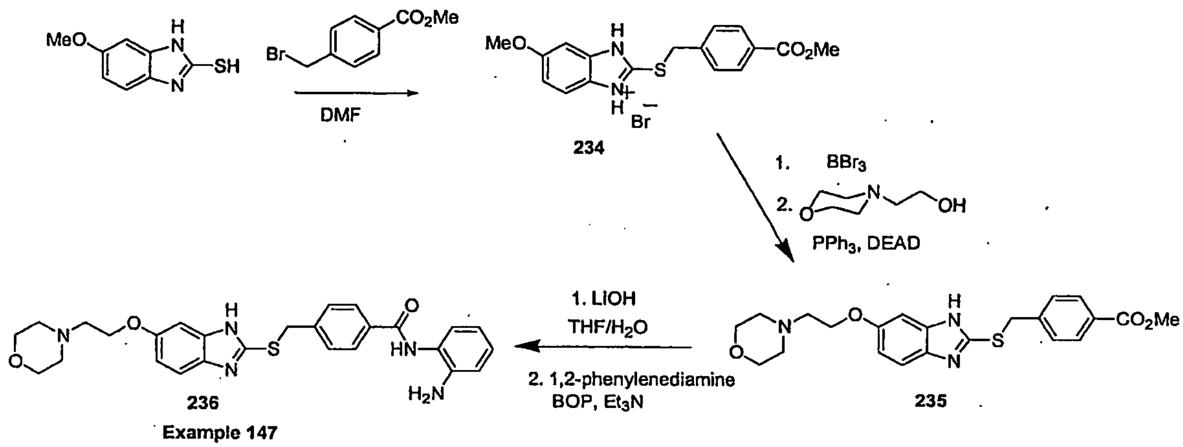
[0293] To a solution of 2-amino-6-methoxybenzothiazole (2.00 g, 11.1 mmol) in a mixture of dichloroethane (20 mL) and THF (20 mL), were successively added methyl 4-formylbenzoate (1.82 g, 11.1 mmol), sodium triacetoxyborohydride (3.53 g, 16.7 mmol) and acetic acid (1.27 mL, 22.2 mmol). The mixture was stirred over 2 days and was quenched by adding aqueous saturated solution of $NaHCO_3$. The mixture was poured in a separating funnel containing water and was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography using EtOAc/ hexane (20:80 to 30:70) to afford the title compound **232** (1.85g, 51% yield). ^{1}H NMR: (Acetone-d_6) δ (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J= 8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J= 8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H).

Step 2: *N*-(2-Amino-phenyl)-4-[(6-methoxy-benzothiazol-2-ylamino)-methyl]-benzamide(**233**):

[0294] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **233** was obtained in 19% yield as a light beige solid. ^{1}H NMR: (DMSO-d_6) δ

(ppm): 9.68 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.00 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.39 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.21 (d, J=6.6 Hz, 1H), 7.05 (t, J=6.3 Hz, 1H), 7.00 (d, J=1.4 Hz, 1H), 6.88 (dd, J=8.8, 2.7 Hz, 1H), 6.86 (dd, J=8.0, 1.4 Hz, 1H), 6.65 (td, J=7.4, 1.4 Hz, 1H), 4.95 (s, 2H), 4.70 (d, J=5.8 Hz, 2H), 3.79 (s, 3H).

Scheme 36



Example 147

Step 1: 4-(6-Methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester hydrobromide (**234**):

[0295] To a solution of methyl 4-(bromomethyl)benzoate (2.51g, 11.0 mmol) in DMF (50 mL) was added 5-methoxy-2-benzimidazolethiol (1.98g, 11.0 mmol). The mixture was stirred at room temperature for 24 h and the solvent was evaporated *in vacuo*. The residue was suspended in ethyl acetate and the hydrobromide salt was collected by filtration to afford the title compound **234** (4.10g, 91% yield) as a colorless solid. ^{1}H NMR: (DMSO-d_6) δ (ppm): 7.90 (d, J= 8.2 Hz, 2H), 7.55 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 1H), 7.03 (s,1H), 6.94 (d, J= 8.2 Hz,1H), 4.65 (s,2H), 3.82 (s,3H), 3.79 (s, 3H).

Step 2:: 4-[6-(2-Morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (**235**):

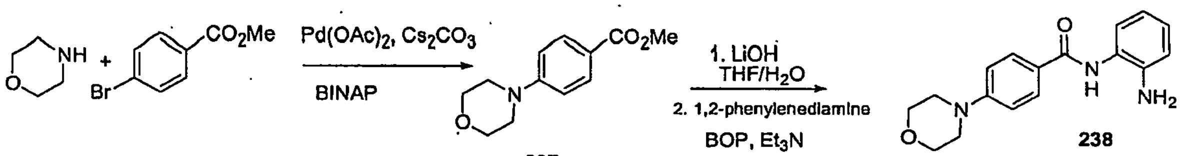
[0296] Following the procedure described in Example 144, step 1, 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound **235** was obtained in 37% yield. ^{1}H NMR: ($CDCl_3$) δ (ppm): 8.04-8.00 (m, 2H), 7.77-7.72 (m, 1H), 7.69-7.59 (m, 1H), 7.56-7.49 (m, 2H), 6.96-6.90 (m, 1H), 4.68

(s, 2H), 4.31-4.16 (m, 4H), 3.97 (s, 3H), 3.98-3.91 (m, 2H), 3.82-3.72 (m, 2H), 2.75-2.47 (m, 4H).

Step 3: N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-ylsulfanylmethyl]-benzamide (236):

[0297] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **236** was obtained in 11% yield. ^1H NMR: (CD_3OD) δ (ppm): 7.89 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 2H), 7.28 (d, J= 8.5 Hz, 1H), 7.19-7.06 (m, 3H), 6.93-6.79 (m, 3H), 4.55 (s, 2H), 4.18 (t, J= 6.3 Hz, 2H), 3.65-3.62 (m, 4H), 2.51 (t, J= 6.6 Hz, 2H), 2.46-2.42 (m, 4H).

Scheme 37



237

238
Example 148

Example 148

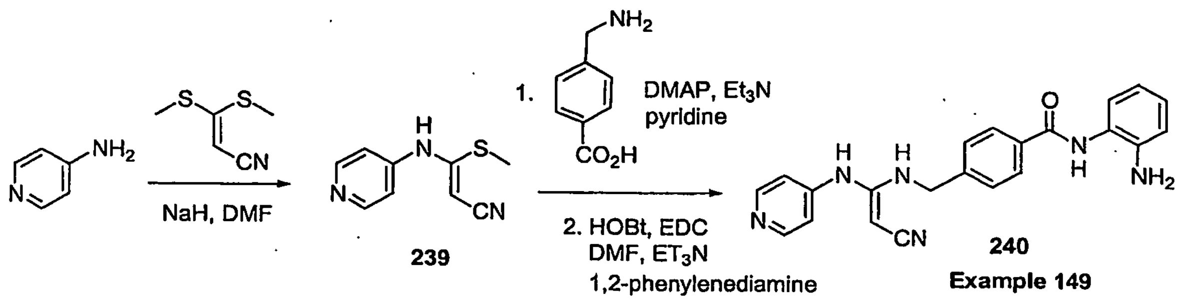
Step 1: 4-Morpholin-4-yl-benzoic acid methyl ester (237):

[0298] A flame-dried pressure vessel was charged with cesium carbonate (912 mg, 2.80 mmol) and toluene (8 mL) and the flasked was purged with nitrogen. Palladium acetate (9.0 mg, 0.004 mmol) and *rac*-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (37 mg, 0.06 mmol). The mixture was degassed and heated at 100°C for 18 h. It was allowed to cool to room temperature and was filtered through celite, rinsed with ethyl acetate and partitioned between ethyl acetate and water. The organic layer was washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **237** (443 mg, 100% yield). ^1H NMR: ($CDCl_3$) δ (ppm): 8.02 (d, J=9.2 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 3.95 (s, 4H), 3.92 (s, 3H), 3.38-3.35 (m, 4H).

Step 2: *N*-(2-Amino-phenyl)-4-morpholin-4-yl-benzamide (238):

[0299] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **238** was obtained in 33 % yield. ^1H NMR: (DMSO-d_6) δ (ppm): 7.20 (d, J= 7.9 Hz, 1H), 7.07 (d, J= 8.8 Hz, 2H), 7.01 (t, J= 7.0 Hz, 1H), 6.83 (d, J= 7.9 Hz, 1H), 6.65 (t, J= 7.5 Hz, 1H), 4.90 (s, 2H), 3.81-3.79 (m, 4H), 3.32-3.28 (m, 4H).

Scheme 38



Example 149

Step 1: 3-Methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (**239**)

[0300] To a solution of pyridin-4-ylamine (1.0 g, 11.0 mmol) and 3,3-Bis-methylsulfanyl-acrylonitrile (2.05 g, 12.6 mmol) in DMF at room temperature, was added powdered 4A molecular sieves. The mixture was stirred for 1 hr. Subsequently the mixture was cooled to 0 °C, 60% NaH dispersion in oil (0.92 g, 23.0 mmol) was added portionwise over 1 hr. and it was stirred at 0 °C for an additional 2 hrs. The cold bath was removed and the mixture was stirred at room temperature for 20 hrs. DMF was removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 25% MeOH/EtOAc) to afford the desired product as an off-white solid (1.9 g, 89%).

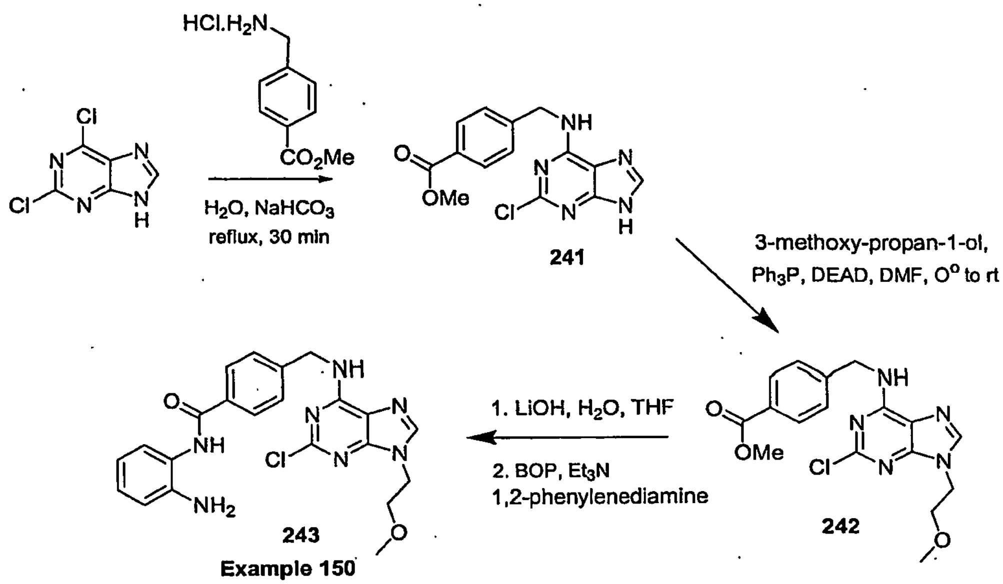
Step 2: *N*-(2-Amino-phenyl)-4-{[2-cyano-1-(pyridin-4-ylamino)-vinylamino]-methyl}-benzamide (**240**)

[0301] To a mixture of 3-methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (0.2 g, 1.0 mmol), 4-aminomethyl-benzoic acid (0.173 g, 1.14 mmol), DMAP (1 mg) and Et_3N (0.14 ml, 1.0 mmol) was added dry pyridine (0.5 ml). The resulting stirring mixture was heated to 55 °C for 4.5 hrs., additional Et_3N (0.14 ml) was added and mixture was heated from 75 °C to 90 °C over a period of ~30 hrs. When the reaction was complete, pyridine was partially removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 20% MeOH/EtOAc) to afford the desired product as an off-white solid (130 mg, 44%).

[0302] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **240** was obtained in 33 % yield. ^{1}H NMR: ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm): 9.69 (br, 2H), 8.48 (br, 3H), 8.03 (d, J = 7.9 Hz, 2H), 7.51

(d, J = 8.4 Hz, 2H), 7.29 (br, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.03 (t, J= 7.0 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H), 4.96 (br, 2H), 4.62 (d, J = 5.7 Hz, 2H).

Scheme 39



Example 150

Step 1: 4-[(2-Chloro-*9H*-purin-6-ylamino)-methyl]-benzoic acid methyl ester (**241**)

[0303] A suspension of 2,6-dichloro-*9H*-purine (1 g, 5.29 mmol), 4-aminomethyl-benzoic acid methyl ester hydrochloride (1.2 equiv., 1.28 g) and $NaHCO_3$ (2.1 equiv., 935 mg) in water was heated at 100°C. The homogeneous solution thus formed was refluxed 30 min. The resulting white precipitate was filtered, washed with cold water and dried under vacuum giving the title compound **241** (1 g, 3.14 mmol, 60%). LRMS calc:317.7, found: 318.3 $(MH)^+$.

Step 2: 4-{[2-Chloro-9-(2-methoxy-ethyl)-*9H*-purin-6-ylamino]-methyl}-benzoic acid methyl ester (**242**)

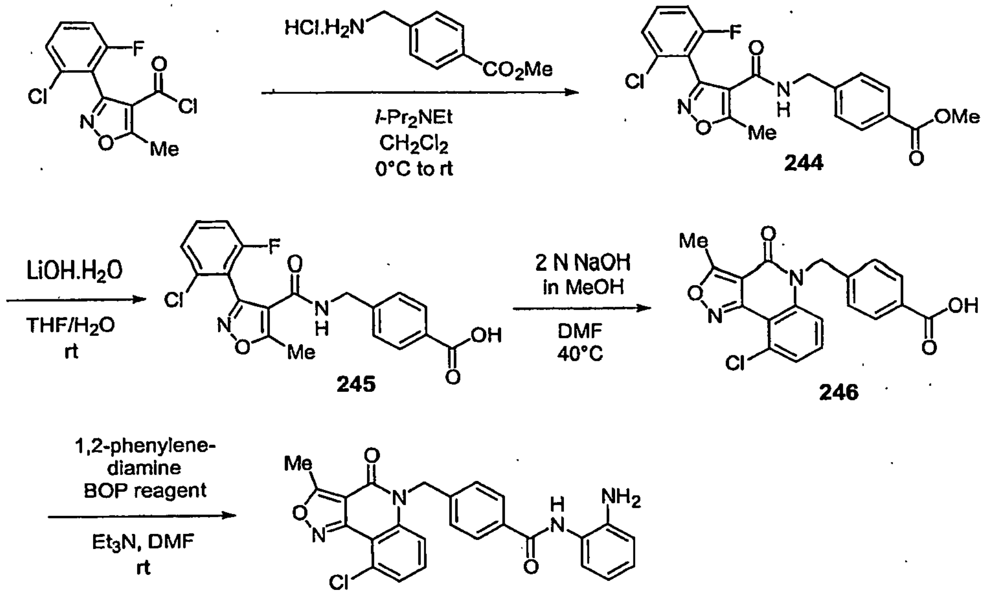
[0304] Following the procedure described in Example 144, step 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound **242** was obtained in 41% yield.

Step 3: *N*-(2-Amino-phenyl)-4-{[2-chloro-9-(2-methoxy-ethyl)-*9H*-purin-6-ylamino]-methyl}-benzamide (**243**):

[0305] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **243**

was obtained in 85% yield. ^1H NMR ($CDCl_3$) δ (ppm): 9.64 (s, 1H), 8.94 (bs, 1H), 8.18 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7,01 (dd, J = 7.3, 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.62 (dd, J = 7.3, 7.7 Hz, 1H), 4.91 (bs, 2H), 4.78 (bs, 2H), 4.18 (m, 2H), 3.70 (m, 2H), 3.26 (s, 3H)

Scheme 40



247
Example 151

Example 151

Step 1: Methyl-4-{[3-(2-chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino-methyl}-benzoic acid ester (**244**)

[0306] To a stirred suspension at 0°C of methyl 4-(aminomethyl)benzoate.HCl **2** (809 mg, 4.01 mmol) in anhydrous CH_2Cl_2 (25 ml) under nitrogen were successively added *i*-Pr_2NEt (1.91 ml, 10.95 mmol) and 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (1.00 g, 3.65 mmol). After 45 min, the reaction mixture was allowed to warm up to room temperature for 3 h. Then, the reaction mixture was concentrated, diluted with AcOEt, and successively washed with *sat.* NH_4Cl, H_2O, *sat.* $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound **244** (1.50 g, quantitative yield) as a colorless sticky foam. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (d, J = 7.9 Hz, 2H), 7.46-7.35 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.15-7.05 (m, 3H), 5.49 (bs, 1H), 4.46 (d, J = 5.7 Hz, 2H), 3.92 (s, 3H), 2.80 (s, 3H).

Step 2: 4-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino-methyl}-benzoic acid (245)

[0307] To a stirred solution at room temperature of **244** (1.45 g, 3.60 mmol) in THF (20 ml) was added a solution of $LiOH.H_2O$ (453 mg, 10.80 mmol) in water (20 ml). After 20 h, the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until pH 6 in order to get a white precipitate. After 10 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **245** (1.23 g, 3.15 mmol, 88% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.69 (t, J = 5.9 Hz, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.70-7.58 (m, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.45-7.30 (m, 3H), 4.44 (d, J = 5.7 Hz, 2H), 2.72 (s, 3H).

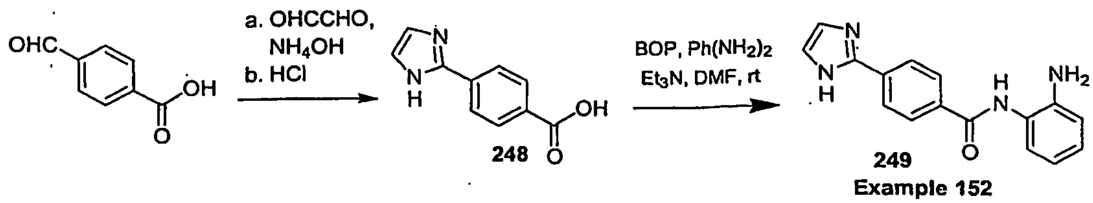
Step 3: 4-(9-Chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzoic acid (246)

[0308] To a stirred suspension at room temperature of **245** (795 mg, 2.05 mmol) in anhydrous DMF (10 ml) was added a solution of NaOH (409 mg, 10.22 mmol) in anhydrous MeOH (5.1 ml). Then, the reaction mixture was warmed up to 40°C. After 3 days, the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until pH 5 in order to get a pale pinky precipitate. After 30 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **246** (679 mg, 1.84 mmol, 90% yield) as a pale pinky solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): AB system (δ_A = 7.92, δ_B = 7.40, J = 8.4 Hz, 4H), 7.56 (t, J = 8.1 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 5.59 (bs, 2H), 2.95 (s, 3H).

Step 4: *N*-(2-Amino-phenyl)-4-(9-chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzamide (247)

[0309] The title compound **247** was obtained from **246** in one step following the same procedure as Example 1, steps 5. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H), AB system (δ_A = 7.95, δ_B = 7.42, J = 8.1 Hz, 4H), 7.58 (t, J = 8.1 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.00 (t, J =7.3 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.62 (t, J = 7.3 Hz, 1H), 5.61 (bs, 2H), 4.91 (s, 2H), 2.97 (s, 3H).

Scheme 41



Example 152

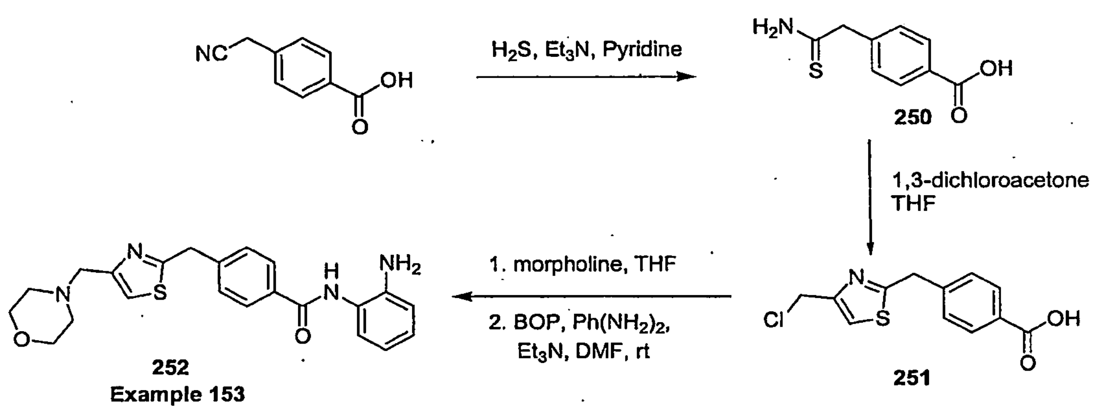
Step 1: 4-(1*H*-Imidazol-2-yl)-benzoic acid (**248**)

[0310] To a stirred solution of 4-formylbenzoic acid (2.00 g, 12.3 mmol) in ammonium hydroxide (9 ml) was added glyoxal (2.86 ml, 20.0 mmol). The reaction mixture was stirred 16 h at room temperature. 1N HCl was added to the reaction mixture to acidify to pH 5. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound **248** (2.08 g, 83%) as a white solid. LRMS: 188.1 (Calc.); 189.1 (found).

Step 2: *N*-(2-Amino-phenyl)-4-(1*H*-imidazol-2-yl)-benzamide (**249**)

[0311] The title compound **249** was obtained following the same procedure as Example 1, step 5. ^{1}H NMR ($CDCl_3$) δ (ppm): ^{1}H NMR: (DMSO) δ (ppm): 9.72 (bs, 1H), 8.07 (s, 4H), 7.26 (s, 2H), 7.18 (d, J = 7.9 Hz, 1H), 6.98 (dd, J = 7.5, 7.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H). MS: (calc.) 278.1; (obt.) 279.1 $(MH)^+$.

Scheme 42



Example 153

Step 1: 4-Thiocarbamoylmethyl-benzoic acid (**250**)

[0312] To a stirred suspension of 4-cyanomethyl-benzoic acid (1.65 g, 10.24 mmol) and Et_3N (5 ml) in pyridine, H_2S was bubbled during 3 h. The reaction mixture was stirred 16 h at room temperature. Water

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was then added to the reaction mixture which was agitated for 1 h before acidifying to pH 6 with 1M HCl. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound **250** (2.08 g, 83%) as a white solid. ^{1}H NMR (DMSO) δ (ppm): 12.85 (bs, 1H), 9.53 (bs, 1H), 9.43 (bs, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 3.88 (s, 2H).

Step 2: 4-(4-Chloromethyl-thiazol-2-ylmethyl)-benzoic acid (**251**)

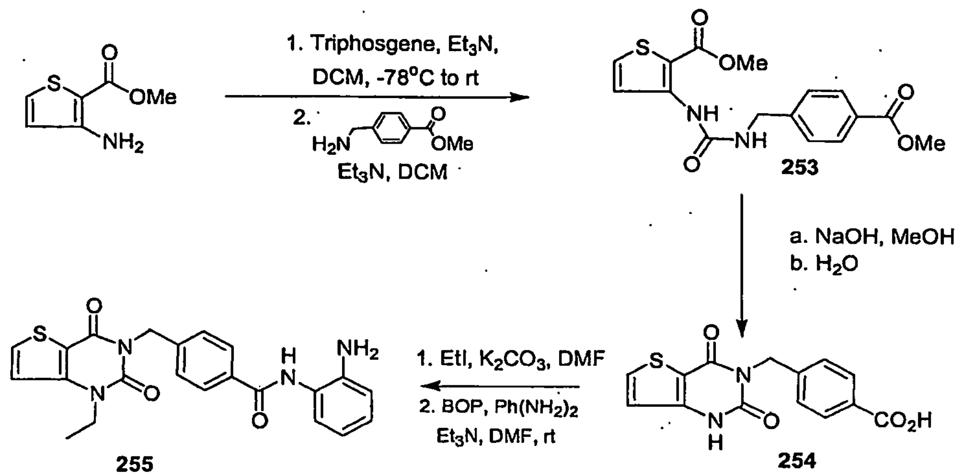
[0313] A solution of **250** (729 mg, 3.73 mmol) and 1,3-dichloroacetone (474 mg, 3.73 mmol) in THF (30 ml) was stirred at 40°C during 48h. The solvent was evaporated then the residue was dissolved in ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (2-4% MeOH/CH_2Cl_2) to afford the title compound (827 mg, 83% yield) as a white solid. ^{1}H NMR (DMSO) δ (ppm): 12.93 (bs, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 4.78 (s, 2H), 4.42 (s, 2H).

Step 3: *N*-(2-Amino-phenyl)-4-(4-morpholin-4-ylmethyl-thiazol-2-ylmethyl)-benzamide (**252**)

[0314] K_2CO_3 (599 mg, 4.33 mmol) was added to a solution of **251** (527 mg, 1.97 mmol) and morpholine (189 □l, 2.17 mmol) in THF (15 ml) was refluxed during 48h. The solvent was evaporated. The crude residue was purified by flash chromatography on silica gel (3-50% MeOH/CH_2Cl_2) to afford the title compound **252** (238 mg, 38% yield) as a pale yellow solid. LRMS: 318.2 (calc) 319.2 (found).

[0315] The title compound **252** was obtained following the same procedure as Example 1, step 5. 1H NMR (DMSO) δ (ppm): 9.63 (bs, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.33 (s, 1H), 7.15 (d, J = 8.1Hz, 1H), 6.97 (dd, J = 7.7, 7.7 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 8.1, 8.1 Hz, 1H), 4.90 (bs, 2H), 4.40 (s, 2H), 3.59-3.56 (m, 6H), 2.44-2.38 (m, 4H). LRMS: 408.2 (calc) 409.2 (found).

Scheme 43



255
Example 154

Example 154

Step 1: Methyl 3-[3-(4-methoxycarbonyl-benzyl)-ureido]-thiophene-2-carboxylate (253)

[0316] The procedure described by Nakao (K. Nakao, R. Shimizu, H. Kubota, M. Yasuhara, Y. Hashimura, T. Suzuki, T. Fujita and H. Ohmizu; *Bioorg. Med. Chem.* **1998**, 6, 849-868.) was followed to afford the title compound **253** (1.01 g, 91%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.55 (bs, 1H), 8.00-7.97 (m, 3H), 7.42-7.37 (m, 3H), 5.45 (t, J = 5.8 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H).

Step 2: 4-(2,4-Dioxo-1,4-dihydro-2*H*-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzoic acid (254)

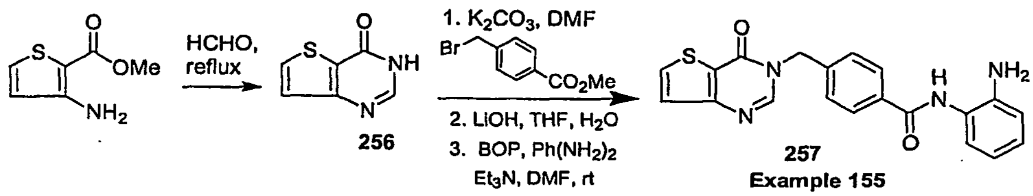
[0317] To a suspension of **253** (422 mg, 1.21 mmol) in MeOH (15 ml) was added NaOH (145 mg, 3.63 mmol). The reaction mixture was heated at 60°C during 16 h. Water (1 ml) was then added and the reaction mixture was stirred for 1 more hour. The solvent was evaporated and the residue was dissolved in water and acidified to pH 5 with HCl 1M. The precipitate was filtered to afford the desired compound **254** (348 mg, 95%) as a white solid. LRMS: 302.0 (Calc.); 303.0 (found).

Steps 3: *N*-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2*H*-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (255)

[0318] The title compound **255** was obtained as a yellow solid (73%) following the same procedure as Example 99, step 2, 3, then followed by Example 1, step 5. ^{1}H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H, *NH*), 8.22 (d, J = 5.5 Hz, 1H, C*H*), 7.91 (d, J = 8.2 Hz, 2H, C*H*), 7.43-7.40 (m,

3H, C*H*), 7.15 (d, *J* = 7.4 Hz, 1H, C*H*), 6.96 (dd, *J* = 7.6, 7.6 Hz, 1H, C*H*), 6.77 (d, *J* = 7.1 Hz, 1H, C*H*), 6.59 (dd, *J* = 7.4, 7.4 Hz, 1H, C*H*), 5.17 (s, 2H, NCH_2), 4.88 (bs, 2H, NH_2) 4.09 (q, *J* = 7.0, 2H, CH_2), 1.22 (t, *J* = 7.0, 3H, CH_3). LRMS: 420.1 (calc.); 421.0 (found).

Scheme 44



Example 155

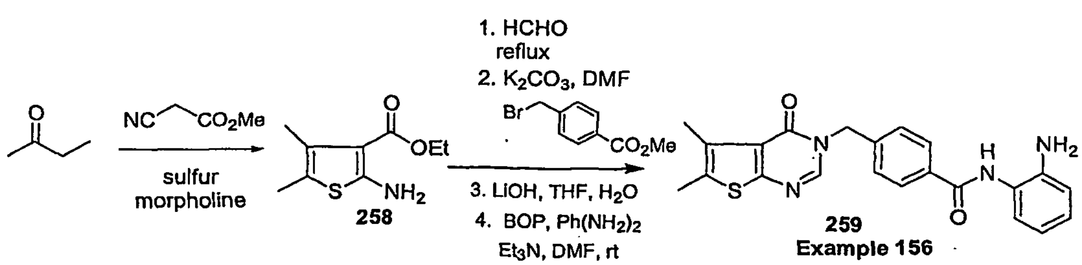
Step 1: 3*H*-Thieno[3,2-d]pyrimidin-4-one (256)

[0319] Methyl-3-amino-2-thiophene carboxylate (510 mg, 3.24 mmol) was dissolved in formamide (20 ml) and heated at 170°C 16h. The solvent was evaporated. The crude residue was then purified by flash chromatography on silica gel (2-4% MeOH/CH_2Cl_2) to afford the title compound **256** (157 mg, 32% yield). LRMS: 152.0 (Calc.); 152.9 (found).

Step 2: *N*-(2-Aminophenyl)-4-(4-oxo-4*H*-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (257)

[0320] Following the procedure described in Example 85, step 1 but substituting the previous compound for **119**, followed by Example 1, step 4, 5, the title compound **257** was obtained in 41% yield. ^{1}H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.70 (s, 1H), 8.22 (dd, *J* = 5.2, 0.5 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.44 (dd, *J* = 5.2, 0.6 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.96 (dd, *J* = 6.9, 6.9 Hz, 1H), 6.77 (d, *J* = 7.1Hz, 1H), 6.58 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.31 (s, 2H), 4.87 (bs, 2H). MS: 376.1 (calc.); 377.1 (found).

Scheme 45



Example 156

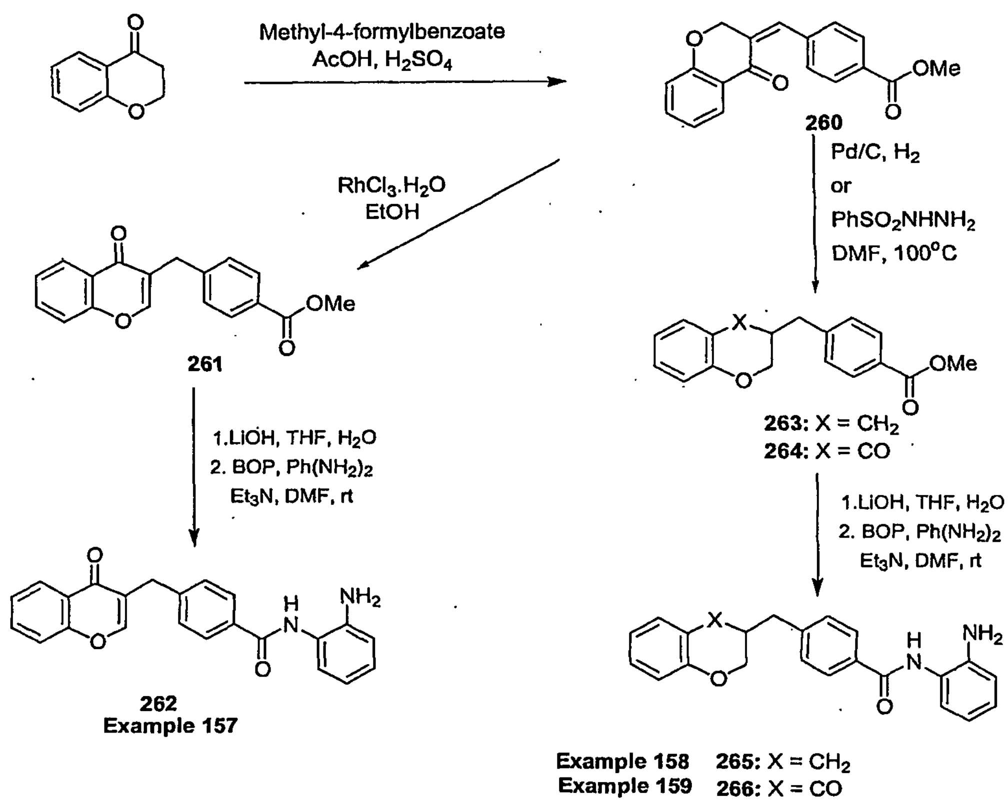
Step 1: Methyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate (258)

[0321] The procedure described by Hozien (Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab and S. A. Ahmed; *Synht. Commun*.. **1996**, 26(20), 3733-3755.) was followed to afford the title compound **258** (1.44 g, 17%) as a yellow solid. LRMS: 197.1 (Calc.); 200.1 (found).

Steps 2: *N*-(2-Amino-phenyl)-4-(5,6-dimethyl-4-oxo-4*H*-thieno[2,3-d]pyrimidin-3-ylmethyl)-benzamide (259)

[0322] Following the procedure described in Example 155, step 1, 2 but substituting **258** for **256**, the title compound **259** was obtained as a white solid (55%). ^{1}H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.57 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 7.7 Hz, 1H), 6.96 (dd, J = 7.6, 7.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.25 (s, 2H), 4.87 (bs, 2H), 2.39 (s, 3H), 2.37 (s, 3H). LRMS: 404.1 (calc); 405.0 (found).

Scheme 46



Example 157

Step 1: Methyl 4-(4-oxo-chroman-3-ylidenemethyl)-benzoate (260)

[0323] Concentrated H_2SO_4 (2 ml) was slowly added to a solution of 4-chromanone (2.00 g, 13.50 mmol) and methyl-4-formylbenzoate (2.11 g, 12.86 mmol) in glacial acetic acid. The reaction mixture was stirred 16 h at room temperature. The solvent was concentrated to half volume the resulting precipitate was filtered and rinsed with ethyl acetate to afford the title compound **260** (3.11 g, 82%) as a purple solid. ^{1}H NMR: (DMSO) δ (ppm): 8.05 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.64-7.59(m, 3H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.43 (s, 2H), 3.89 (s, 3H).

Step 2: Methyl-4-(4-oxo-4H-chromen-3-ylmethyl)-benzoate (261)

[0324] Water (0.2 ml) and $RhCl_3.H_2O$ (7 mg, 0.034 mmol) was added to a suspension of compound **260** (200 mg, 0.680 mmol) in EtOH (2 ml) and $CHCL_3$ (2 ml). The reaction mixture was stirred 16 h at 70°C. The reaction mixture was cooled down and diluted in ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (0.5-1% $MeOH/CH_2Cl_2$)to afford the title compound **261** (118 mg, 59%) as a white solid. ^{1}H NMR: (DMSO) δ (ppm): 8.45 (s, 1H), 8.03 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.83-7.77(m, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.50-7.43 (m3, 1H), 3.82 (s, 3H), 3.80 (s, 2H).

Step 3: *N*-(2-Amino-phenyl)-4-(4-oxo-4H-chromen-3-ylmethyl)-benzamide (262)

[0325] The title compound **262** was obtained following the same procedure as Example 1, step 4, 5. ^{1}H NMR: (DMSO) δ (ppm): 9.56 (bs, 1H), 8.45 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.80 (dd, J = 7.5, 7.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.51-7.42 (m, 3H), 7.14 (d, J = 7.9 Hz, 1H), 6.96 (dd, J = 7.3, 7.3 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (dd, J = 7.3, 7.3 Hz, 1H), 4.86 (bs, 2H), 3.80 (s, 2H). LRMS: 370.1 (calc.); 371.1 (found).

Example 158

Step 2: Methyl 4-chroman-3-ylmethyl-benzoate (263)

[0326] Pd/C 10% was added to a suspension of **260** (200 mg, 0.68 mmol) in MeOH (40 ml) and DMA (10 ml) which was previously purged

under vacuum. The reaction mixture was stirred during 4 h at room temperature. After evaporation of the MeOH, water was added to the oily residue and the precipitate obtained was filtered. The crude residue was then purified by flash chromatography on silica gel (5-8% AcOEt/Hex)to afford the title compound **263** (114 mg, 59%) as a white solid. LRMS: 282.1 (Calc.); 283.0 (found).

Step 3: *N*-(2-Amino-phenyl)-4-chroman-3-ylmethyl-benzamide (**265**)

[0327] The title compound **265** was obtained following the same procedure as Example 1, steps 4 and 5. ^{1}H NMR: (acetone) δ (ppm): 9.06 (bs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.08-6.98 (m, 3H), 6.87 (d, J = 7.5 Hz, 1H),6.82-6.66 (m, 3H), 4.62 (s, 2H), 4.22-4.17 (m, 1H), 4.88-3.81 (m, 1H), 2.88-2.71 (m, 3H), 2.61-2.53 (m, 1H), 2.41-2.33 (m, 1H). LRMS: 358.2 (calc.); 359.1 (found).

Example 159

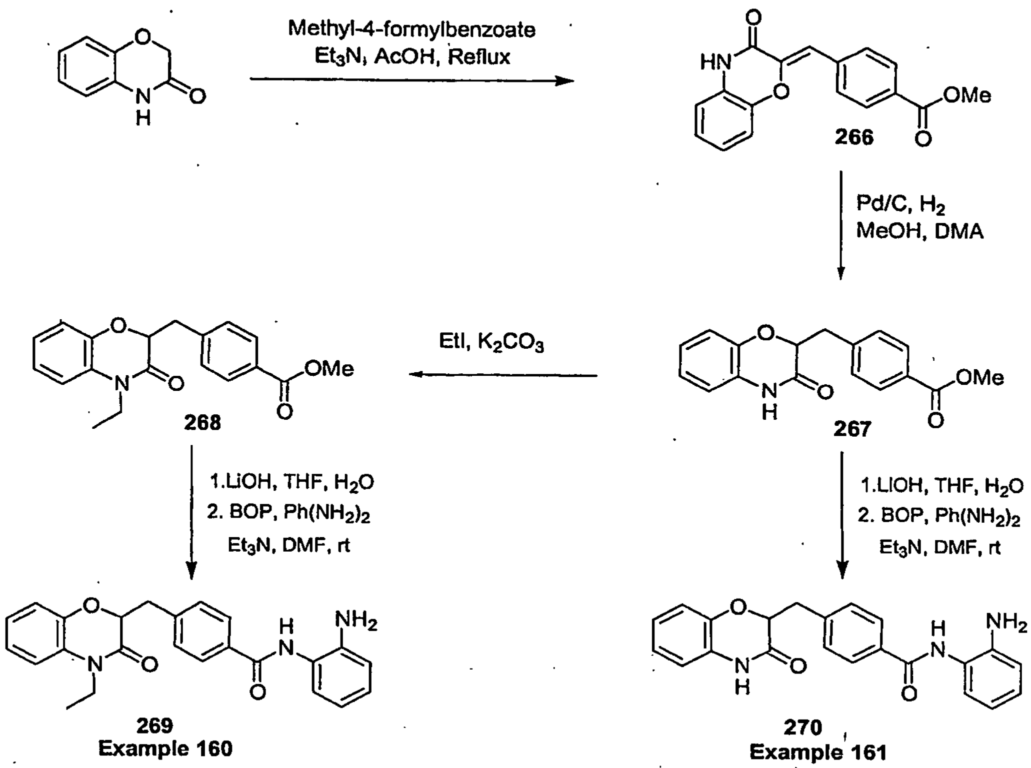
Step 2: Methyl 4-(4-oxo-chroman-3-ylmethyl)-benzoate (**264**)

[0328] A suspension of **260** (400 mg, 1.36 mmol) and benzenesulfonyl hydrazine (702 mg, 4.08 mmol) in DMF (7 ml) was stirred at 100°C during 48h. The solvent was evaporated and the residue was diluted in AcOEt, washed with NH_4Cl sat., brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5% AcOEt/HEx)to afford the title compound **264** (170 mg, 42%) as a white solid. LRMS: 296.1 (Calc.); 297.0 (found).

Step 3: *N*-(2-Amino-phenyl)-4-(4-oxo-chroman-3-ylmethyl)-benzamide (**266**)

[0329] The title compound **266** was obtained following the same procedure as Example 1, steps 4 and 5. ^{1}H NMR: (acetone) δ (ppm): 9.62 (bs, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.0, 7.0 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.17-7.04 (m, 3H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H), 4.88 (s, 2H), 4.44-4.39 (m, 1H), 4.28-4.21 (m, 1H), 2.26-3.21 (m, 2H), 2.83-2.74 (m, 1H). LRMS: 372.1 (calc.); 372.1 (found).

Scheme 47



Example 160

Step 1: Methyl 4-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-ylmethyl)-benzoate (**266**)

[0330] Et_3N (3.18 ml, 22.8 mmol) was added to a stirring solution of 2-*H*-1,4-benzoxazin-3-(4*H*)one (2.50 g, 16.8 mmol) and methyl 4-formylbenzoate (4.59 g, 27.5 mmol) in Ac_2O (20 ml). The reaction mixture was refluxed 16h. After this mixture was cooled for 3 days, the solid was filtered and rinsed with ethyl acetate to afford the title compound **266** (657 mg, 13%) as a yellow solid. LRMS: 295.1 (Calc.); 296.0 (found).

Step 2: Methyl 4-(3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylidenemethyl)-benzoate (**267**)

[0331] The title compound **267** was obtained following the same procedure as Example 158, step 2. LRMS: 297.1 (Calc.); 298.1 (found).

Step 3: *N*-(2-Amino-phenyl)-4-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzamide (**269**)

[0332] The title compound **269** was obtained from **267** following the same procedure as Example 99, step 2, 3, then followed by Example 1,

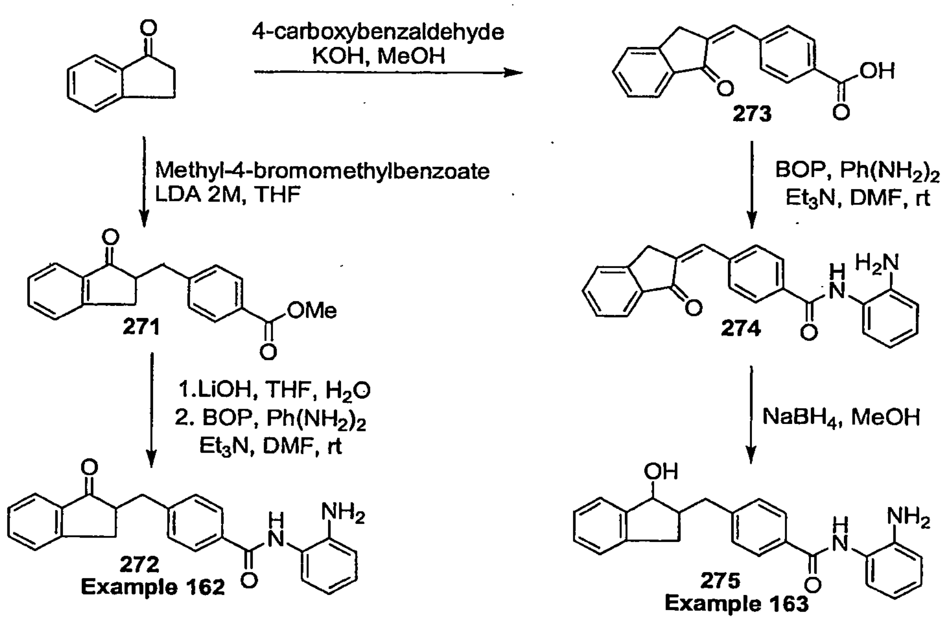
step 4, 5. ^{1}H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.22 (d, J =7.9 Hz, 1H), 7.17 (d, J =7.5 Hz, 1H), 7.11-6.91 (m, 4H), 6.77 (d, J = 7.0 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.95-4.91 (m, 1H), 4.89 (bs, 2H), 3.95 (q, J = 7.0 Hz, 2H), 3.28-3.22 (m, 1H), 3.17-2.89 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H). LRMS: 401.2 (calc.); 402.1 (obt.).

Example 161

Step 1: *N*-(2-Amino-phenyl)-4-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-ylmethyl)-benzamide (270)

[0333] The title compound **270** was obtained from **267** following the same procedure as Example 1, step 4, 5. ^{1}H NMR: (DMSO) δ (ppm): 10.74 (bs, 1H), 9.61 (bs, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.17 (d, J =7.5 Hz, 1H), 6.99-6.85 (m, 5H), 6.78 (d, J = 7.5 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.92-4.89 (m, 3H), 3.29-3.23 (m, 1H), 3.15-3.07 (m, 1H). MS: (calc.) 373.1; (obt.) 374.1 (MH)$^+$.

Scheme 48



Example 162

Step 1: Methyl 4-(1-oxo-indan-2-ylmethyl)-benzoate (271)

[0334] A 2M LDA solution in THF (4.16 ml, 8.32 mmol) was added to a solution of indanone (1.00 g, 7.57 mmol) in THF (10 ml) at -60°C. The solution was slowly warmed to 0°C during a period of 15 min. and was

agitated for 15 more min. The reaction was then cooled to -78°C and a solution of methyl-4-bromobenzoate (1.73 g, 7.57 mmol) was slowly added. The solution was slowly warmed to -20°C and stirred during 4 hours. The reaction mixture was quenched with HCL 1M and the solvent was evaporated. The residue was diluted in ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5-20% AcOEt/HEx)to afford the title compound **271** (245 mg, 17%) as a white solid. LRMS: 280.1 (Calc.); 281.1 (found).

Step 2: *N*-(2-Amino-phenyl)-4-(1-oxo-indan-2-ylmethyl)-benzamide (272)

[0335] The title compound **272** was obtained following the same procedure as Example 1, step 4, 5. ^1H NMR: (DMSO) δ (ppm): 9.59 (bs, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.69-7.64 (m, 2H), 7.54 (d, J =7.6 Hz, 1H), 7.45-7.40 (m, 3H), 7.16 (d, J = 8.2 Hz, 1H), 6.96 (dd, J = 7.3, 7.3 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 4.87 (bs, 2H), 3.23-3.14 (m, 3H), 2.85-2.81 (m, 2H). LRMS: 356.1 (calc.); 357.2 (found).

Example 163

Step 1: 4-(1-Oxo-indan-2-ylidenemethyl)-benzoic acid (273)

[0336] To a suspension of indanone (2.00 g, 15.1 mmol) and 4-carboxybenzaldehyde (1.89g, 12.6 mmol) in EtOH (10 ml) was added KOH (1.77 g , 31.5 mmol) at 0°C. The reaction mixture was stirred 30 min at 0°C then at room temperature for 16 h. The solvent was evaporated and the residue was dissolved in water, acidified to pH 5 with HCl 1 M. The precipitate was filtered and rinsed with water to afford the title compound **273** (2.27 g, 57%) as a yellow solid. LRMS: 264.1 (Calc.); 265.0 (found).

Step 2: *N*-(2-Amino-phenyl)-4-(1-oxo-indan-2-ylidenemethyl)-benzamide (274)

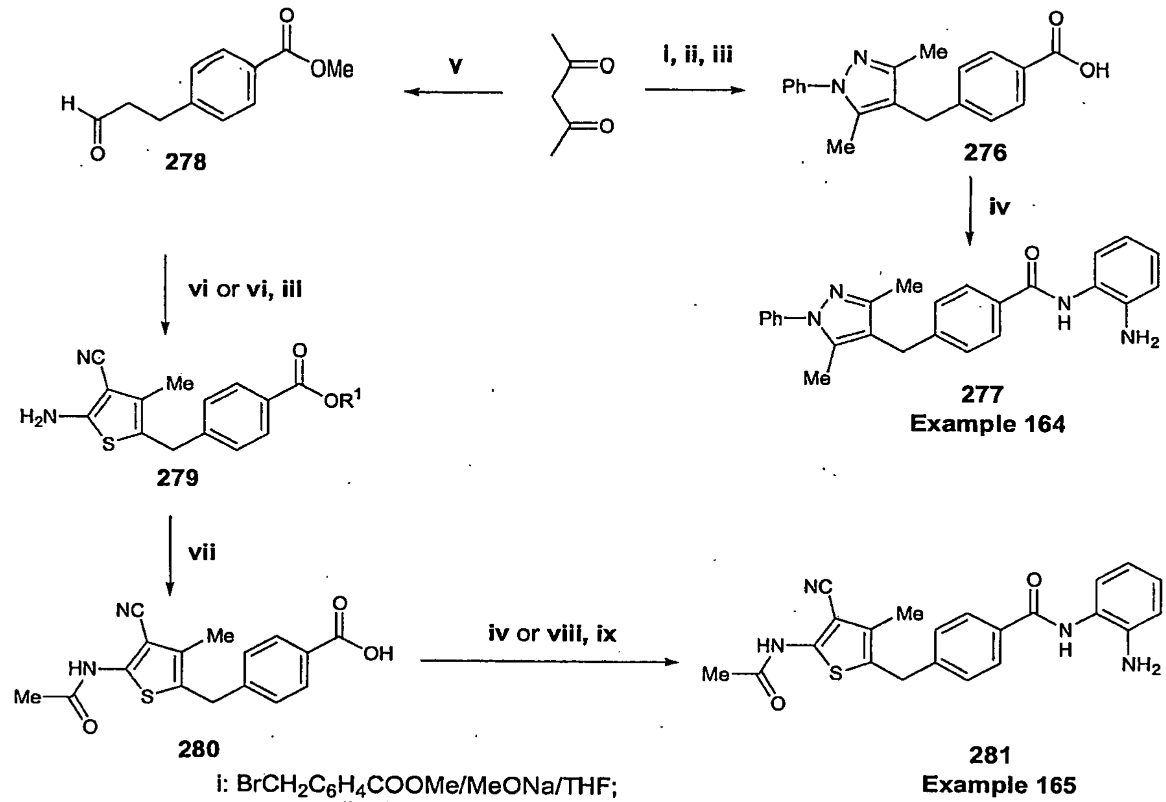
[0337] The title compound **274** was obtained following the same procedure as Example 1, step 5. LRMS: 354.1 (Calc.); 355.0 (found).

Step 3: *N*-(2-Amino-phenyl)-4-(1-hydroxy-indan-2-ylmethyl)-benzamide (275)

[0338] To a suspension of **274** (300 mg, 0.85 mmol) in MeOH (8 ml) and water (1 ml) was added $NaBH_4$ (75 mg, 1.95 mmol). The reaction mixture was stirred at 50°C 16h and cooled down. Water was added to

the solution and the precipitated was filtered and rinsed with cold water to afford the title compound **275** (224 mg, 74%) as a white solid. ^{1}H NMR: (acetone) δ (ppm): 9.05 (bs, 1H), 8.00 (dd, J = 8.2, 2.7 Hz, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.43 (d, J =8.2 Hz, 1H), 7.38-7.30 (m, 2H), 7.22-7.12 (m, 3H), 7.01 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.87 (dd, J = 8.0, 1.1 Hz, 1H), 6.68 (dd, J = 7.6, 7.6 Hz, 1H), 4.98 (t, J = 5.8 Hz, 0.4H), 4.89 (t, J = 6.7 Hz, 0.6H), 4.63 (bs, 2H), 4.45 (d, J = 6.9 Hz, 0.6H), 4.06 (d, J = 6.0 Hz, 0.4H), 3.30-3.19 (m, 1H), 2.88-2.48 (m, 3H, CH_2). LRMS: 358.2 (calc.); 359.1 (found).

Scheme 49



i: $BrCH_2C_6H_4COOMe$/MeONa/THF;
ii: $PhNHNH_2$;
iii: NaOH, then HCl
iv: HOBt/EDC.HCl then 1,2-diaminobenzene;
v: $BrCH_2C_6H_4COOMe$/MeONa/MeOH, then HCl/AcOH;
vi: $CH_2(CN)_2/S_8/Et_2NH$(or Et_3N);
vii: AcCl, PhCOCl or PhNCO;
viii: 2-*N*-Bocamino aniline;
ix: TFA;

Example 164

Step 1: 4-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-benzoic acid (276)

[0339] To a solution of NaH (60% in mineral oil, 250 mg, 6.3 mmol) at 0°C acetyl acetone (0.646 ml, 6.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester **2** (1.2 g, 5.2 mmol). The reaction mixture stirred 1 hour at room temperature and refluxed for 2 hours. Phenyl hydrazine (0.51 ml, 5.2 mmol) was added and the reaction mixture refluxed for an additional hour. THF was removed in vacuum and the oily residue was partitioned between water and ethyl acetate. Organic layer was separated, dried, evaporated and purify by chromatography on a silica gel column, eluent EtOAc - hexane (1:1) to produce an oily material (800mg) which was treated with a solution of NaOH (0.8 g, 20 mmol) in 20 ml water for 1 hour at room temperature. The following steps, - acidification with HCl (pH 6), extraction of the resultant emulsion with ethyl acetate, drying the extract with sodium sulfate, evaporation and column chromatography (eluent EtOAc - hexane, 1:1) afforded 390 mg of a mixture of **276** (the title compound) and **278** (molar ratio 1:2). $[M-1]^+$ 307.0 and 191.1. This mixture was taken for the next step as is.

Step 2. *N*-(2-Amino-phenyl)-4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-benzamide (277)

[0340] Following a procedure analogous to that described in Example 92, step 2, but substituting **276** for **143**, the title compound **277** was obtained in 25% yield (purified by chromatography using as eluent EtOAc - hexane, 1:1). ^{1}H NMR: (300 MHz, DMSO-d_6, δ (ppm): 9.64 (s, 1H); 7.97 (d, J = 7.6 Hz, 2H), 7.42-7.56 (m, 5H), 7.37 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 4.93 (s, 2H), 3.92 (s, 2H), 2.34 (s, 3H), 2.18 (s, 3H).

Example 165

Step 1: 4-(3-Oxo-butyl)-benzoic acid (278)

[0341] To a solution of acetyl acetone (5.0 ml, 49 mmol) at room temperature NaOMe (25% wt, 10.8 ml, 47.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester **2** (9.0 g, 39.3 mmol). The reaction mixture refluxed 3 hours, cooled to the room temperature and acidified with HCl (pH 1-2). Evaporation of the resultant

solution yielded a residue, which was refluxed in a mixture of glacial AcOH (50 ml) and conc. HCl (25 ml) for 4 hours. Acids were removed in vacuum and the residue was triturated with water to form a crystalline material, which was collected by filtration and dried to afford **278** (6.72 g, 80% yield). [M-1] 191.1.

Step 2. 4-(5-Amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 279

[0342] To a refluxing suspension of 4-(3-oxo-butyl)-benzoic acid **278** (700 mg, 3.65 mmol), malonodinitrile (241 mg, 3.65 mmol) and sulfur (130 mg, 3.65 mmol) in 20 ml EtOH, diethylamine (0.5 ml, 4.8 mmol) was added. The reaction mixture refluxed 1 hour, cooled to the room temperature, acidified with conc. HCl (pH 4-5) and evaporated to yield a solid residue. This material was partitioned between water and ethyl acetate, organic layer was separated, dried, evaporated and chromatographed on a silica gel column, eluent EtOAc-hexane, 1:1, to afford the title compound **279** (300 mg, 30% yield). ^{1}H NMR: (300 MHz, DMSO-d_6, δ ppm): 7.87 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.98 (s, 2H), 3.92 (s, 2H), 2.03 (s, 3H).

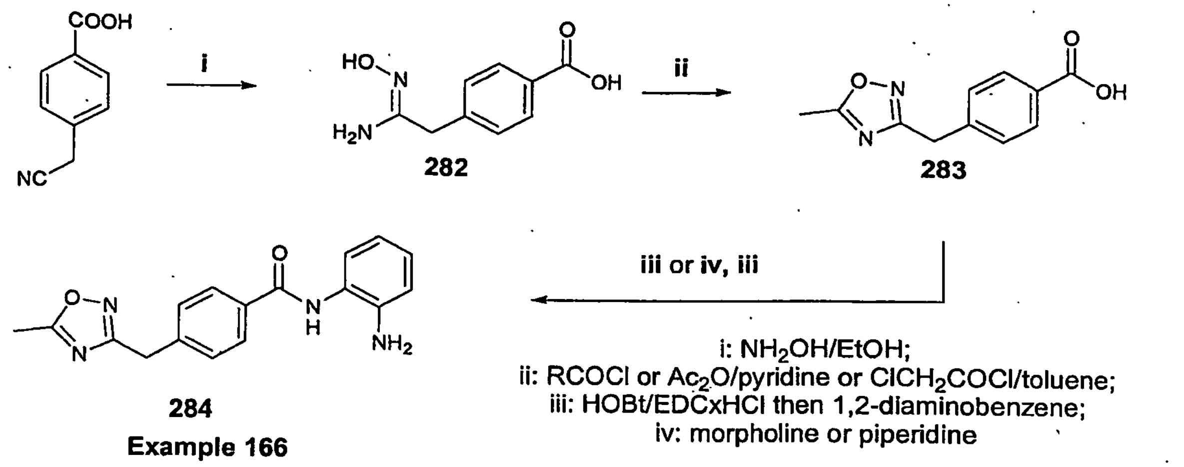
Step 3. 4-(5-Acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 280

[0343] To a solution of 4-(5-amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid **279** (230 mg, 0.86 mmol) in a solvent mixture acetone (5 ml) - dichloromethane (5 ml) at room temperature acetyl chloride (0.305 ml, 4.3 mmol) was added. After 2 hours of stirring at the same conditions a precipitate of the title compound **280** formed which was collected and dried (200 mg, 75% yield). [M-1] 313.1.

Step 4: *N*-(2-Amino-phenyl)-4-(5-acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)- benzamide (281)

[0344] Following a procedure analogous to that described in Example 92, step 2, but substituting **280** for **143**, the title compound **281** was obtained in 25% yield. 1H NMR (DMSO) δ (ppm): 9.61 (s, 1H); 7.91 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 6.6 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.10 (s, 2H), 2.19 (s, 3H), 2.16 (s, 3H). [M+1] 405.0.

Scheme 50



Example 166

Step 1. 4-(*N*-Hydroxycarbamimidoylmethyl)-benzoic acid (**282**)

[0345] A suspension of 4-cyanomethyl benzoic acid (2.07 g, 12.86 mmol), $NH_2OH.HCl$ (1.79 g, 25.71 mmol) and potassium hydroxide (2.16 g, 38.57 mmol) in 70 ml ethanol refluxed for 36 hours, poured into 100 ml water and acidified with conc. HCl (pH 5-6). EtOH was removed in vacuum and the remaining suspension was treated with another 100 ml water. A precipitate formed which was collected and dried to afford the title compound **282**. [M+1]195.1.

Step 2. 4-(5-Methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzoic acid (**283**)

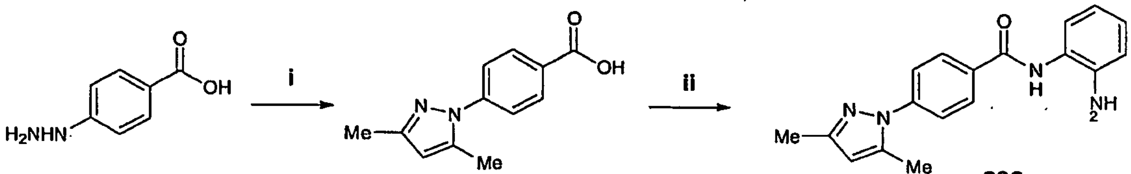
[0346] A solution of 4-(*N*-hydroxycarbamimidoylmethyl)-benzoic acid 282 (388 mg, 2.0 mmol) in pyridine (8 ml) was treated with acetic anhydride (0.283 ml, 3.0 mmol). The resultant solution refluxed 6 hours, evaporated in vacuum and the remaining solid was triturated with water, collected by filtration, dried and purified by chromatography on a silica gel column, eluent EtOAc, EtOAc-MeOH (10:1) and finally EtOAc-MeOH (1:1), to produce 283 (164 mg, 38% yield). $[M-1]^-$ 217.1

Step 3. N-(2-Amino-phenyl)-4-(5-methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide (**284**)

[0347] For the preparation of the title compound **284**, a procedure analogous to that described in Example 92, step 2, but substituting **283** for **143**, the title compound **284** was obtained. ^{1}H NMR: (DMSO) δ (ppm): 9.62 (s, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.9 Hz, 1H), 6.78 (d, J

= 7.5 Hz, 1H), 6.60 (t, J = 7.9 Hz, 1H), 4.92 (s, 2H), 4.14 (s, 2H), 2.55 (s, 3H). $[M+1]^+$ 309.2

Scheme 51



285

286
Example 167

i: Acetyl acetone/EtOH;
ii: HOBt/EDCxHCl then 1,2-diaminobenzene;

Example 167

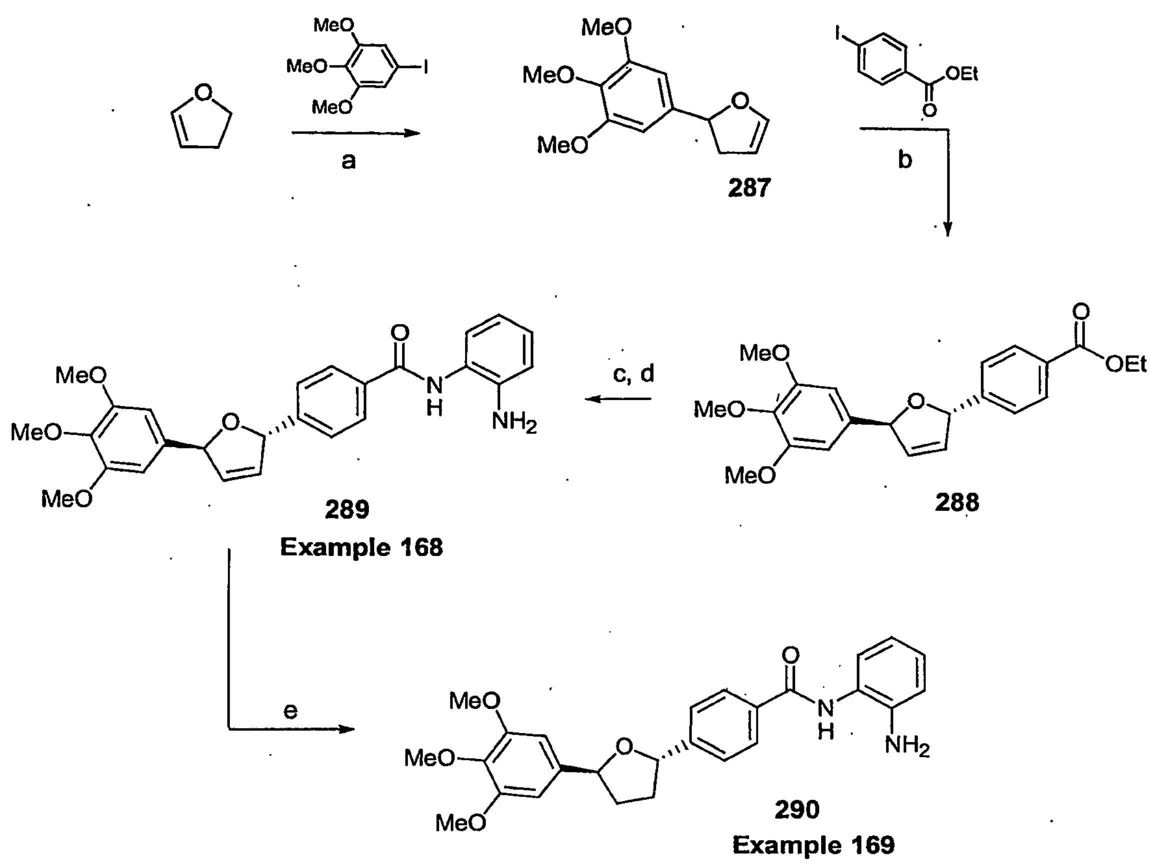
Step 1: 4-(3,5-Dimethyl-pyrazol-1-yl)-benzoic acid (**285**)

[0348] A solution of 4-hydrazino-benzoic acid (0.60 g, 3.95 mmol) and acetyl acetone (0.405 ml, 3.95 mmol) in ethanol (20 ml) refluxed for 1 hour. Ethanol was removed in vacuum and the remaining solid was triturated with water and collected by filtration to produce **285** (0.71 mg, 83% yield). $[M-1]^-$ 215.1.

Step 2. N-(2-Amino-phenyl)-4-(3,5-dimethyl-pyrazol-1-yl)-benzamide (**286**)

[0349] For the preparation of the title compound **286**, a procedure analogous to that described in Example 92, step 2, but substituting **285** for **143**, the title compound **286** was obtained in 34% yield (purified by chromatography using as eluent CH_2Cl_2-methanol, 19:1). ^1H NMR: (DMSO) δ (ppm): 9.73 (s, 1H); 8.09 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 6.13 (s, 1H), 4.92 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H). $[M+1]^+$ 303.3

Scheme 52



a. 2.5% $Pd(OAc)_2$ / nBu_4NCl (1 eq) / KOAc (3 eq) / 2.5% PPh_3 / DMF / 80°C
b. 3-4% $Pd(OAc)_2$ / 9% PPh_3 / Ag_2CO_3 (2 eq) / CH_3CN / 80°C
c. LiOH · H_2O / THF-H_2O (2:1)
d. 1,2-phenylenediamine / BOP / Et_3N / DMF
e. PtO_2 / H_2 (1 atm) / AcOEt

Example 168

Step 1: 2-(3,4,5-Trimethoxy-phenyl)-2,3-dihydro-furan (287)

[0350] To a solution of 5-iodo-1,2,3-trimethoxybenzene (900 mg, 3.06 mmol) and 2,3-dihydrofuran (1.16 mL, 15.3 mmol) in dry DMF (8 mL) were added PPh_3 (20 mg, 0.077 mmol), KOAc (901 mg, 9.18 mmol), *n*-Bu_4NCl (850 mg, 3.06 mmol) and $Pd(OAc)_2$ (17 mg, 0.077 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was diluted with AcOEt and water. After separation, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 20/80) to afford the title compound **287** (311 mg, 1.32 mmol, 43% yield). ^1H NMR: (300 MHz, $CDCl_3$) δ (ppm): 6.59 (s, 2H), 6.45 (m, 1H), 5.45 (dd, J = 10.5, 8.4

Hz, 1H), 4.97 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.06 (m, 1H), 2.62 (m, 1H).

Step 2: 4-[5-(3,4,5-Trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzoic acid ethyl ester (288)

[0351] To a solution of **287** (200 mg, 0.846 mmol) and 4-Iodo-benzoic acid ethyl ester (468 mg, 1.69 mmol) in dry acetonitrile (4 mL) were added PPh_3 (20 mg, 0.076 mmol), Ag_2CO_3 (467 mg, 1.69 mmol) and $Pd(OAc)_2$ (7 mg, 0.03 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was filtered through celite and washed with AcOEt. Water was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 30/70) to afford the title compound **288** (280 mg, 0.728 mmol, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.05 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 6.61 (s, 2H), 6.18-5.95 (m, 4H), 4.38 (q, J = 7.0 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 1.39 (t, J = 7.0 Hz).

Step 3: *N*-(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzamide (289)

[0352] Following a procedure analogous to that described in Example 1, step 4, 5, but substituting **288** for **6**, the title compound **289** was obtained in 48% yield. ^{1}H NMR (DMSO) δ (ppm): 8.00 (s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.92-6.82 (m, 2H), 6.61 (s, 2H), 6.14-5.99 (m, 4H), 3.89 (s, 6H), 3.84 (s, 3H).

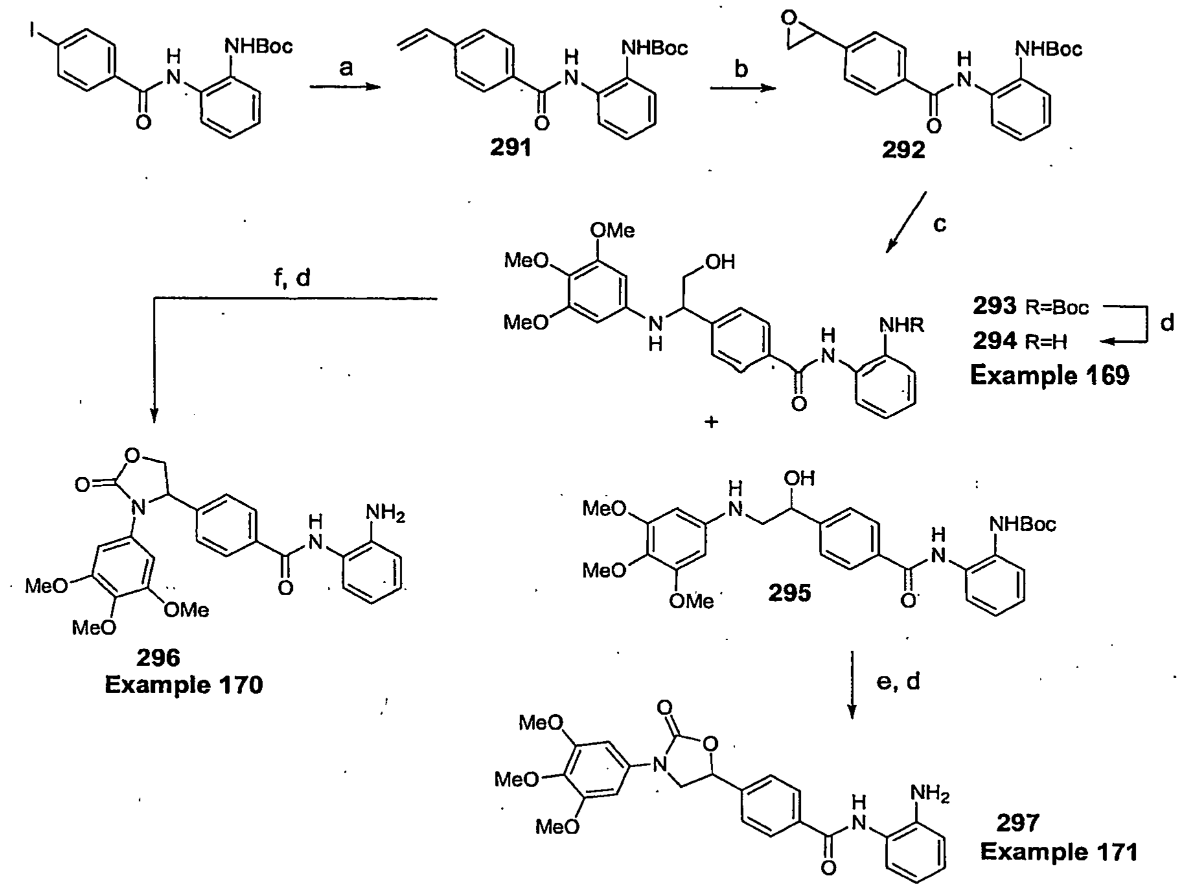
Example 169

Step 1: *N*-(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzamide. (290)

[0353] To a degazed solution of **289** (43 mg, 0.096 mmol) in AcOEt (4 mL) was added PtO_2 (3 mg, 0.01 mmol) and the reaction mixture was stirred at room temperature under a 1 atm pressure of H_2 for 16 h. The reaction flask was purged with N_2 then the reaction mixture was filtered through celite, rinsed with MeOH and concentrated. The crude residue was purified three times by flash chromatography on silica gel (MeOH/DCM: 2/98, AcOEt/DCM: 30/70 and AcOEt/$CHCl_3$: 30/70) to afford the title compound **290** (10 mg, 0.22 mmol, 23% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.10 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H),

6.96-6.85 (m, 2H), 6.64 (s, 2H), 5.33 (t, J = 7.0 Hz, 1H), 5.21 (t, J = 7.0 Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 2.59-2.40 (m, 2H), 2.09-1.88 (m, 2H).

Scheme 53



a. Tributyl(vinyl)tin / $Pd(PPh_3)_4$ / Toluene / 100°C
b. *m*-CPBA / $CHCl_3$ / r.t.
c. 3,4,5-trimethoxyaniline / $CoCl_2$ / CH_3CN
d. TFA / DCM
e. 1,1'-carbonyldiimidazole / DCM / r.t.
f. 1,1'-carbonyldiimidazole / Et_3N / Toluene / THF / 90°C

Example 169

Step 1: [2-(4-Vinyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (291)

[0354] Following a procedure analogous to that described in Example 143, step 2, but substituting **184** for **221**, the title compound **291**

was obtained in 90% yield as a dark yellow oil. ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm): 9.18 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.30-7.10 (m, 3H), 6.89 (s, 1H), 6.77 (dd, J = 17.4, 11.0 Hz, 1H), 5.87 (d, J = 17.4 Hz, 1H), 5.39 (d, J = 11.0 Hz, 1H), 1.52 (s, 9H).

Step 2: [2-(4-Oxiranyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (**292**)

[0355] To a solution of **291** (4.1 g, 12.1 mmol) in dry $CHCl_3$ (60 mL) was added *m*-CPBA 70% (3.6 g, 14.5 mmol). The reaction mixture was stirred at room temperature for 5 h then additional *m*-CPBA (0.6 g, 2.4 mmol) was added and the stirring continued for 1 h. A further amount of *m*-CPBA (0.6 g, 2.4 mmol) was added and the reaction mixture was stirred for 16 h. Chloroform and a 10% solution of $NaHCO_3$ were added and the phases were separated. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 1/3) to afford the title compound **292** (2.86 g, 8.07 mmol, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.20 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.86-7.75 (m, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.26-7.10 (m, 3H), 6.84-6.70 (m, 1H), 3.93 (t, J = 3.0 Hz, 1H), 3.20 (t, J = 5.0 Hz, 1H), 2.80 (dd, J = 5.0, 3.0 Hz, 1H), 1.52 (s, 9H).

Step 3: (2-{4-[1-Hydroxy-2-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (**295**) and (2-{4-[2-Hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid *tert*-butyl ester (**293**)

[0356] To a stirred solution of $CoCl_2$ (8 mg, 0.06 mmol) in dry acetonitrile (10 mL) was added **292** (1 g, 2.8 mmol) followed by 3,4,5-trimethoxyaniline (516 mg, 2.8 mmol) and the reaction mixture was allowed to react for 16 h at room temperature then it was heated at 60°C for 5 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/Hexane: 1/1) to afford compounds **293** and **295** (combined: 1.07 g, 1.99 mmol, 71% yield, ratio **292/295** = 5/1) which can be separated by flash chromatography on silica gel (AcOEt/Hexane: 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): Compound **292**:

9.21 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 6.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.28-7.10 (m, 3H), 6.90 (s, 1H), 5.83 (s, 2H), 4.54-4.44 (m, 1H), 3.93 (dd, J = 8.1, 3.9 Hz, 1H), 3.84-3.72 (m, 1H), 3.71 (s, 3H), 3.66 (s, 6H), 1.47 (s, 9H). Compound **295**: 9.22 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.30-7.21 (m, 3H), 6.88 (s, 1H), 6.15 (s, 2H), 5.16-5.06 (m, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.50-3.25 (m, 2H), 1.51 (s, 9H).

Step 4: *N*-(2-Amino-phenyl)-4-[2-hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzamide (**294**)

[0357] Following a procedure analogous to that described in Example 42, step 3, but substituting **293** for **46**, the title compound **294** was obtained in 50% yield. ^{1}H NMR (DMSO) δ (ppm): 8.36 (s, 1H), 7.74 (d, J = 6.9 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.72 (m, 2H), 5.69 (s, 2H), 4.34 (m, 1H), 4.02-3.52 (m, 2H), 3.66 (s, 3H), 3.57 (s, 6H).

Example 170

Step 1: *N*-(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-4-yl]-benzamide (**296**)

[0358] To a solution of **293** (200 mg, 0.372 mmol) in toluene (5 mL) and THF (1 mL) was added 1,1'-carbonyldiimidazole (72 mg, 0.45 mmol) followed by Et_3N (156 μL, 1.12 mmol) and the mixture was stirred at room temperature for 5 h then at 90°C for 48 h. The reaction mixture was diluted with AcOEt, a solution of *sat.* NH_4Cl was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (DCM/AcOEt: 80/20) to afford the desired compound (120 mg, 0.21 mmol, 57% yield). ^{1}H NMR (DMSO) δ (ppm): 9.37 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.25-15 (m, 3H), 6.88 (s, 1H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.79 (t, J = 8.7 Hz, 1H), 4.19 (dd, J = 8.7, 6.0 1H), 3.75 (s, 3H), 3.72 (s, 6H), 1.47 (s, 9H).

[0359] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **296** was obtained in 81% yield.). ^{1}H NMR (DMSO) δ (ppm): 8.03 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H),

7.30 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.5 Hz, 2H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.78 (t, J = 8.7 Hz, 1H), 4.18 (dd, J = 8.7, 6.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 6H).

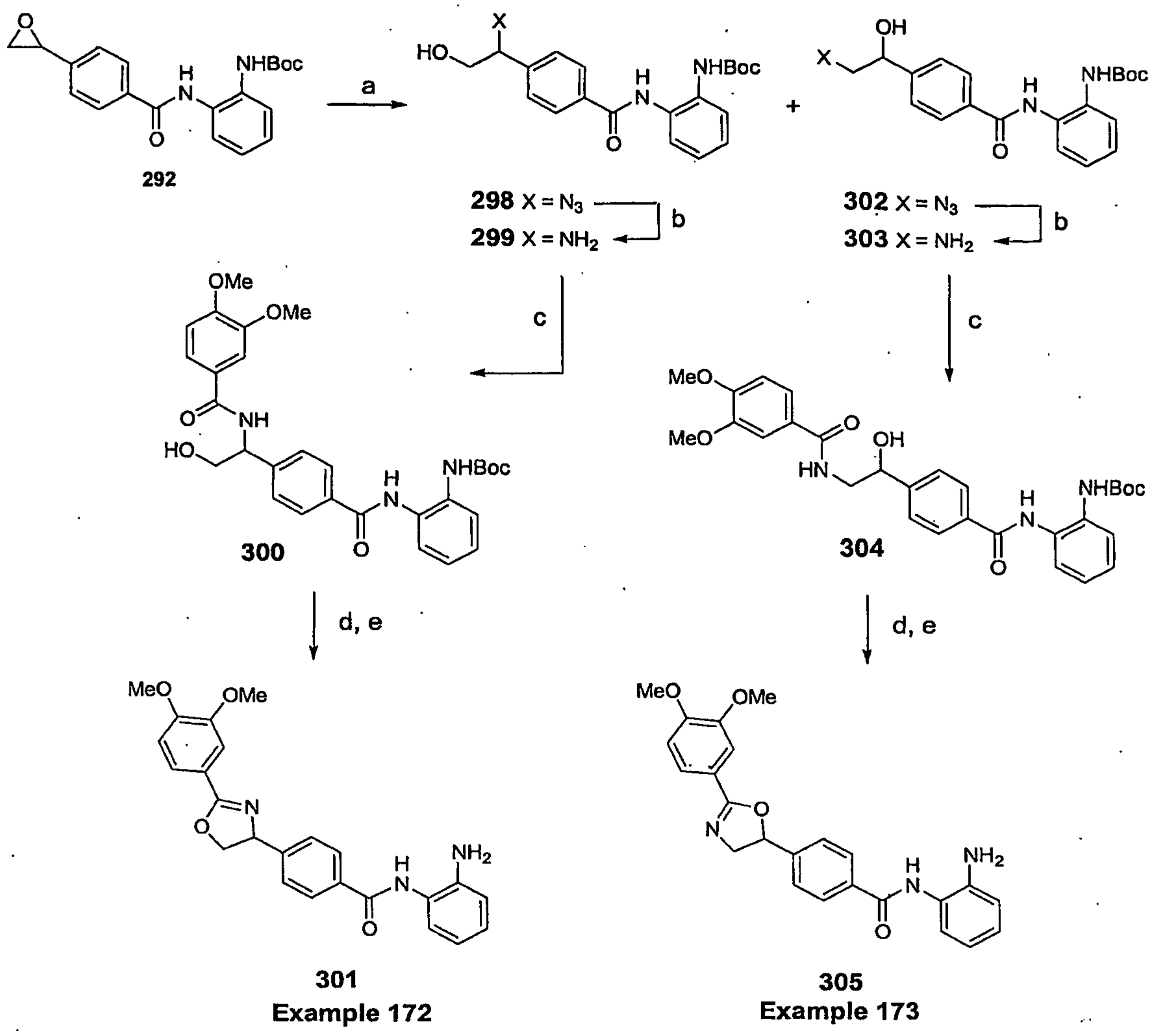
Example 171

Step 1: *N*-(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-5-yl]-benzamide (**297**)

[0360] To a solution of **295** (130 mg, 0.242 mmol) in DCM (2 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol) and the mixture was stirred at room temperature for 16 h. DCM was removed under reduced pressure, AcOEt and a solution of *sat*. NH_4Cl were added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (Hexane/AcOEt: 30/70) to afford the desired compound (80 mg, 0.14 mmol, 58% yield). ^1H NMR (DMSO) δ (ppm): 9.39 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.26-7.12 (m, 3H), 6.86-6.74 (m, 3H), 5.70 (t, J = 8.4 Hz, 1H), 4.24 (t, J = 8.7 Hz, 1H), 3.97-3.87 (m, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 1.52 (s, 9H).

[0361] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **297** was obtained in 94% yield.). ^1H NMR (DMSO) δ (ppm): 8.38 (s, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 7.08 (t, J = 7.0 Hz, 1H), 6.97-6.87 (m, 2H), 6.79 (s, 2H), 5.66 (t, J = 8.1 Hz, 1H), 4.41 (t, J = 9.0 Hz, 1H), 3.91 (t, J = 7.8 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H).

Scheme 54



a. $CeCl_3$ heptahydrate / NaN_3 / CH_3CN - H_2O (9 :1) / reflux

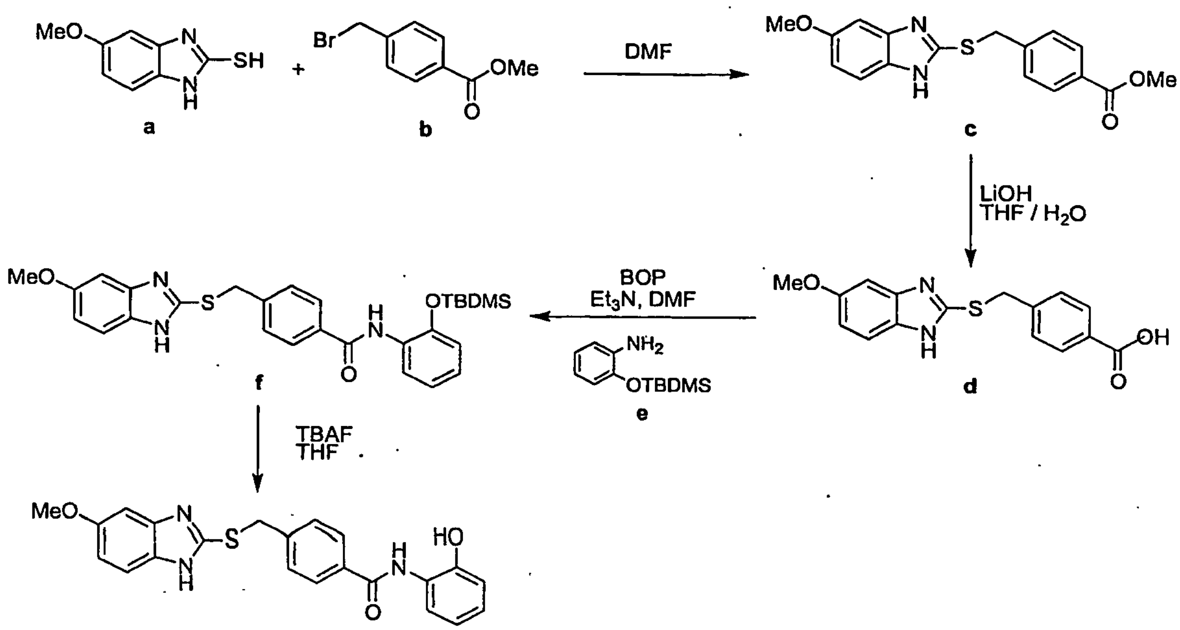
b. H_2 / Pd/C (10%) / MeOH

c. 3,4-dimethoxybenzoyl chloride / Et_3N / DCM / -20°C to r.t.

d. Burgess reagent / THF / 70°C

e. TFA / DCM

Scheme 55



MG 5833X

Example 172

Step 1: {2-[4-(1-Azido-2-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (298) and {2-[4-(2-Azido-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (302)

[0362] To a solution of **292** (210 mg, 0.59 mmol) in acetonitrile (9 mL) and water (1 mL) was added $CeCl_3$ heptahydrate (110 mg, 0.296 mmol) followed by NaN_3 (42 mg, 0.65 mmol). The reaction mixture was refluxed for 3 h then acetonitrile was removed under reduced pressure. The residue was diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash chromatography on silica gel (AcOEt/Hexane: 1/1) afforded a 1:1 mixture of title compounds **298** and **302** (combined: 187 mg, 0.47 mmol, 80% yield) which were separated by flash chromatography on silica gel (AcOEt/Hexane: 2/5). Compound **298**: ^1H NMR: (300 MHz, $CDCl_3/CD_3OD$) δ (ppm): 7.95 (d, J = 8.1 Hz, 2H), 7.70-7.63 (m, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.36-7.29 (m, 1H), 7.24-7.14 (m, 2H), 4.69 (dd, J = 7.5, 4.8 Hz, 1H), 3.80-3.65 (m, 2H), 1.49 (s, 9H). Compound **302**: ^1H NMR: (300 MHz, $CDCl_3$) δ (ppm): 9.28 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.25-7.08 (m, 3H), 7.01 (s, 1H), 4.87 (dd, J = 6.9, 5.1 Hz, 1H), 3.47-3.38 (m, 2H), 3.32-3.21 (bs, 1H), 1.50 (s, 9H).

Step 2: {2-[4-(1-Amino-2-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (299)

[0363] To a solution of **298** (156 mg, 0.39 mmol) in MeOH (2 mL) was added Pd/C 10% (20 mg, 0.02 mmol). The reaction mixture was stirred under a 1 atm pressure of H_2 at room temperature for 16 h then it was purged with N_2. The palladium was removed by filtration through celite and the MeOH was evaporated under reduced pressure to afford the title compound **299** (88 mg, 0.24 mmol, 60% yield), which was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.24 (s, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 6.6 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.31-7.10 (m, 3H), 7.06-6.94 (m, 1H), 4.12 (dd, J = 7.5, 4.5 Hz, 1H), 3.74 (dd, J = 7.8, 5.4 Hz, 1H), 3.64-3.51 (m, 1H), 2.64 (s, 3H), 1.49 (s, 9H).

Step 3: (2-{4-[1-(3,4-Dimethoxy-benzoylamino)-2-hydroxy-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (300)

[0364] To a stirred solution of **299** (88 mg, 0.24 mmol) in dry DCM (2 mL) at -20°C was added 3,4-dimethoxybenzoyl chloride (50 mg, 0.25 mmol) followed by Et_3N (37 μL, 0.26 mmol). The reaction mixture was allowed to warm up to room temperature then was stirred for 48 h. A solution of *sat.* NH_4Cl was added, followed by DCM and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 4/96) to afford title compound **300** (91 mg, 0.17 mmol, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.29 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.65-7.58 (m, 1H), 7.46 (m, 7H), 6.80 (d, J = 8.1 Hz, 1H), 5.20-5.10 (m, 1H), 3.95-3.78 (m, 2H), 3.88 (s, 3H) 3.84 (s, 3H), 1.47 (s, 9H).

Step 4: N-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-4-yl]-benzamide (301)

[0365] To a solution of **300** (91 mg, 0.17 mmol) in dry THF (2 mL) was added the Burgess reagent (44 mg, 0.19 mmol) and the mixture was stirred at 70°C for 2 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 3/97) to afford the Boc-protected intermediate (75 mg, 0.14 mmol, 85% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.31 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.5

Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 6.0 Hz, 1H), 7.23-7.08 (m, 3H), 6.93 (d, J = 8.7 Hz, 1H), 5.43 (t, J = 9.0 Hz, 1H), 4.84 (t, J = 9.3 Hz, 1H), 4.26 (t, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.50 (s, 9H).

[0366] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **301** was obtained in 82%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.01 (s, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.65 (dd, J = 8.4, 1.5 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.08 (t, J = 6.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 5.43 (dd, J = 9.7, 8.4 Hz, 1H), 4.83 (dd, J = 9.7, 8.4 Hz, 1H), 4.25 (t, J = 8.1 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H).

Example 173

Step 1: {2-[4-(2-Amino-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (303)

[0367] The title compound **303** was obtained in 94% yield from **302** following the same procedure as in Example 172, step 2. The compound **303** was used directly for next step without purification.

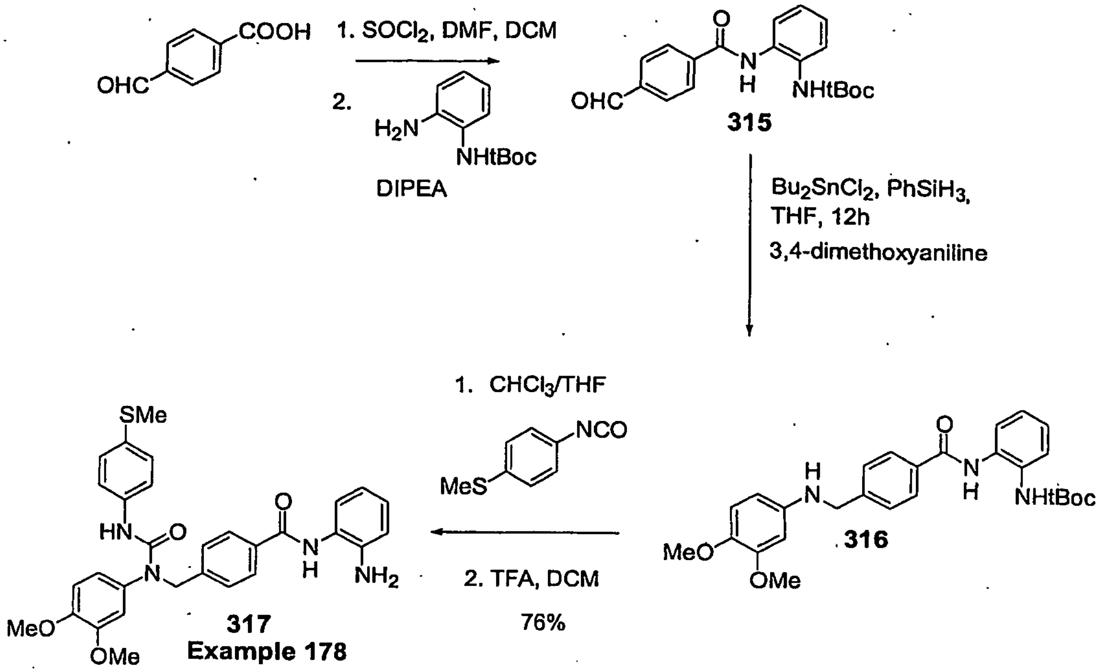
Step 2: 2-{4-[2-(3,4-Dimethoxy-benzoylamino)-1-hydroxy-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (304)

[0368] The title compound **304** was obtained in 40% yield from **303** and 3,4-dimethoxybenzoyl chloride following the same procedure as in Example 172, step 3. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.31 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 8.1 Hz), 7.30-7.06 (m, 4H), 7.00-6.93 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.89-4.82 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85-3.73 (m, 1H), 3.44-3.32 (m, 1H), 1.46 (s, 9H).

Step 3: *N*-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-5-yl]-benzamide (305)

[0369] Following a procedure analogous to that described in Example 172, step 4, 5, but substituting **304** for **300**, the title compound **305** was obtained in 63%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.02 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 8.4, 1.8 Hz, 1H), 7.60 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 2H), 5.74 (dd, J = 10.0, 7.8 Hz, 1H), 4.51 (dd, J = 14.5, 10.0 Hz, 1H), 4.00-3.90 (m, 7H).

Scheme 57



Example 178

STEP 1: [2-(4-FORMYL-BENZOYLAMINO)-PHENYL]-CARBAMIC ACID *TERT*-BUTYL ESTER (315)

[0370] To a suspension of 4-carboxybenzaldehyde (6 g, 40 mmol) in dichloromethane (10 mL) was added thionyl chloride (4.1 mL, 56 mmol, 1.4 eq), followed by DMF (1 mL) dropwise. The mixture was refluxed for 4 hours and excess of thionyl chloride and DMF were removed under reduced pressure. To a solution of (2-aminophenyl)-carbamic acid tert-butyl ester (8.32 g, 40 mmol, 1 eq) in dichloromethane (80 mL), stirred at 0°C, was added a suspension of 4-formyl benzoyl chloride in dichloromethane (20 mL), followed by diisopropyl ethylamine (3.61 mL, 20 mmol, 1 eq). The mixture was stirred for 30 minutes at 0°C then at room temperature for 30 minutes. The crude residue was diluted with dichloromethane (300 mL) and washed with water. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuo. The crude residue was purified by column chromatography on silica gel (elution 20% ethyl acetate in hexane) to give 6.1 g (45% yield) of anilide **315**. ^1H NMR ($CDCl_3$): δ 10.18 (s, 1H), 9.64 (brs, 1H), 8.20 (d, J = 7.9 Hz, 2H), 8.06 (d, J = 7.9 Hz, 2H), 7.96 (d, J = 7.9 Hz, 1H), 7.28-7.38 (m, 1H), 7.24 (d, J = 4.4 Hz, 1H), 6.84 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 1.58 (s, 9H).

Step 2: (2-{4-[(3,4-Dimethoxyphenylamino)-Methyl]-Benzoylamino}-Phenyl)-Carbamic Acid *Tert*-Butyl Ester (316)

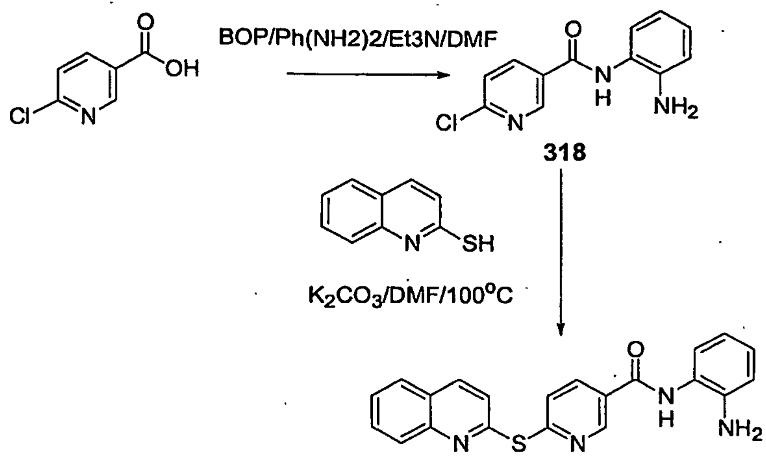
[0371] Following a procedure analogous to that described in Example 144, step 3, but substituting the previous compound for 226, the title compound **316** was obtained in quantitative yield. ^{1}H NMR ($CDCl_3$): δ 9.21 (brs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.86 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.20-7.34 (m, 3H), 6.89 (brs, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 6.23 (dd, J = 2.6, 8.3 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.58 (s, 9H).

Step 3: *N*-(2-Aminophenyl)-4-[1-(3,4-dimethoxyphenyl)-3-(4-methylsulfanylphenyl)-ureidomethyl]-benzamide 317

[0372] To a solution of anilide **316** (500 mg, 1.047 mmol) in chloroform/THF (1:1, 10 mL) was added isocyanate (169 µL, 1.205 mmol, 1.15 eq). The mixture was stirred overnight at room temperature under nitrogen and the crude residue was concentrated and purified by column chromatography on silica gel (elution 40% ethyl acetate in hexane) to give 606 mg (90% yield) of the desired compound. ^{1}H NMR ($CDCl_3$): δ 9.25 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.20-7.36 (m, 6H), 6.93 (d, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 2.2, 8.3 Hz, 1H), 6.68 (dd, J = 2.6 Hz, 1H), 6.33 (s, 1H), 5.0 (s, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 2.51 (s, 3H), 1.57 (s, 9H).

[0373] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **317** was obtained in 85% yield. ^{1}H NMR (DMSO-d_6): δ 10.14 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.93 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39 (d, J = 7.5 Hz, 1H), 7.10-7.30 (2m, 5H), 6.97 (dd, J = 2.2, 8.35 Hz, 1H), 6.77 (dd, J = 2.2, 8.35 Hz, 1H), 5.02 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.48 (s, 3H).

Scheme 58



Example 179

Example 179

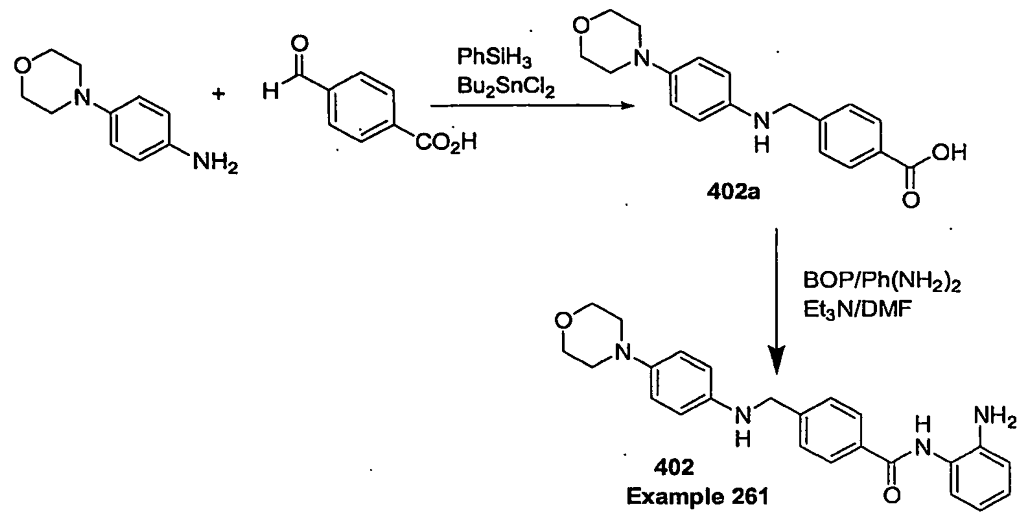
Step 1: *N*-(2-Amino-phenyl)-6-chloro-nicotinamide (**318**)

[0374] Following the procedure described in Example 42, step 2, the title compound **318** was obtained in 80% yield. LRMS = calc:246.69, found:247.7.

Step 2: *N*-(2-Amino-phenyl)-6-(quinolin-2-ylsulfanyl)-nicotinamide (**319**)

[0375] Following the procedure described in Example 45, step 1 but substituting **318** for 3,4,5-trimethoxybenzylamine, the tite compound **319** was obtained in 20% yield. ^{1}H NMR: (CD_3OD-d6) δ (ppm): 9.08 (d, J= 1.9 Hz, 1H), 8.35-8.25 (m, 2H), 7.99-7.56 (m, 7H), 7.23 (dd, J = 1.2, 7.9 Hz, 1H), 7.12 (dd J=1.4, 7.9, 14.0 Hz, 1H), 6.93 (dd, J=1.2, 8.0Hz, 1H), 6.79 (ddd, J=1.4, 7.7, 13.7 Hz, 1H).

Scheme 59



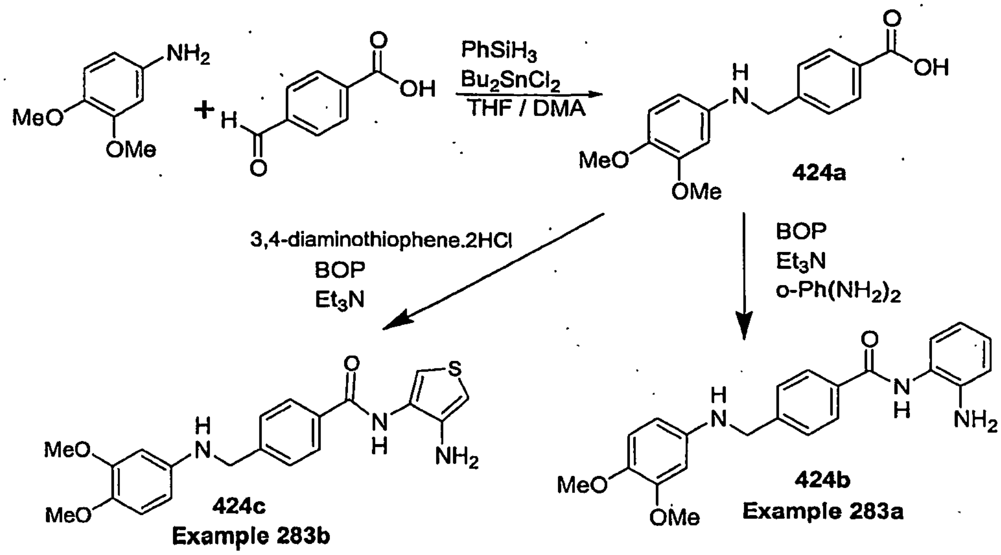
Step 1: 4-[(4-Morpholin-4-yl-phenylamino)-methyl]-benzoic acid (402a).

[0376] A suspension of 4-formylbenzoic acid (2.53g; 16.8 mmol; 1 eq), 4-morpholinoaniline (3g; 16.8 mmol; 1 eq) and Bu_2SnCl_2 (510 mg; 1.68 mmol; 0.1 eq) in dry THF (20 ml) was treated with $PhSiH_3$ (3.31ml; 16.8 mmol; 1 eq) at room temperature for 12 h. The reaction was filtered and the solid product was washed with MeOH. The yield of the reaction was 5.25g (99%). LRMS: calc 312.37; found: 313.2.

Step 2: *N*-(2-Amino-phenyl)-4-[(4-morpholin-4-yl-phenylamino)-methyl]-benzamide (402)

[0377] To a solution of acid **402a** (2.61g; 8,36 mmol; 1 eq), 1,2-phenylenediamine (903 mg; 8.36 mmol; 1 eq) and BOP (3.70g; 8.36 mmol; 1 eq) in dry DMF (20 ml) was added Et_3N (4.64ml; 33.4 mmol; 4 eq). After stirring overnight most of the DMF was removed under reduced pressure and chromatographed (Hex:EtAcO: 1:2/ EtAcO). The crystal **402** was obtained in 70% (2.35g). ^{1}H-NMR (300.07 MHz; DMSO-*d6*) δ (ppm): 9.65 (s, 1H), 7.97 (d, J=7.9, 2H), 7.53 (d, J=7.9, 2H), 7.22 (d, J=7.5, 1H), 7.03 (dd, J=7.0, 7.5, 1H), 6.83 (d, J=7.9, 1H), 6.77 (d, J=8.8, 2H), 6.65 (dd, J=7.5, 7.0,1H), 6.57 (d, J=8.8, 2H), 4.93 (bs, 2H), 4.36 (d, J=5.7, 2H), 3.75 (m, 4H), 2.93 (m, 4H). LRMS: calc 402.49; found: 403.4.

Scheme 60



Example 283a

Step 1. 4-[(3,4-Dimethoxyphenylamino)-methyl]-benzoic acid (**424a**)

[0378] In a 50 ml flask, a mixture of 4-aminoveratrole (1.53 g, 10 mmol), 4-formyl-benzoic acid (1.50 g, 10 mmol), dibutyltin dichloride (304 mg, 1 mmol), phenylsilane (2.47 ml, 20 mmol) in anhydrous THF (10 mL) and DMA (10 ml) was stirred overnight. at room temperature. After solvents removal, the crude residue was dissolved in ethyl acetate (100 ml) and then washed with saturated aqueous solution of $NaHCO_3$ (50 ml x 3) . The combined aqueous layers were acidified with 6% of $NaHSO_4$ to pH = 4. The resulting white suspension was filtrated and then the filter cake was washed with water (5 ml x 3). The cake was dried over freeze dryer to afford acid (1.92 g, 67 %) white solid product. LRMS = 288 $(MH)^+$.

Step 2. N-(2-Aminophenyl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide (**424b**)

[0379] In a 150 ml flask, a mixture of acid (1.92 g, 6.69 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 3.26 g, 7.37 mmol), triethylamine (1.87 ml, 13.4 mmol), *o*-phenylenediamine (1.30g, 12.02 mmol) in methylenechloride (67 ml) was stirred at rt for 2 h. After solvents removal, the crude residue was dissolved in EtOAc (100 ml) and then washed with $NaHCO_3$ saturated solution and brine 50 ml. The combined organic layers were dried over Na_2SO_4 and the filtrate was concentrated to dryness. The crude material was submitted to a chromatographic purification (column silica, 55%-70 % EtOAc in 1%

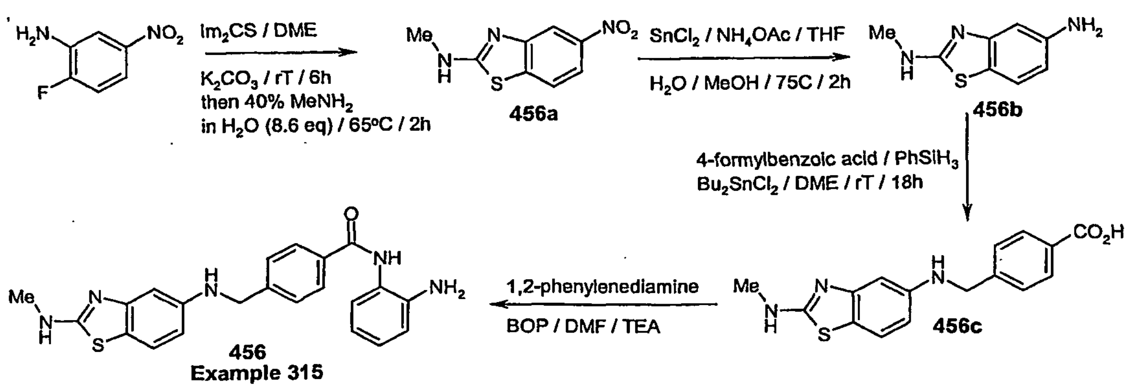
Et_3N of hexanes) and then the all interested fractions were concentrated to dryness. The residue was suspended in minimum quantities of ethyl acetate and then filtered to afford final product (1.49 g, 59 %). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.9, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.5, 7.5 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NH_2), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).

Example 283b

Step 1: N-(4-Aminothiophen-3-yl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide:

[0380] Acid **424a** (1040 mg; 3.62 mmol); 3,4-diaminothiophene dihydrochloride (1017 mg; 5.44 mmol; 1.50 eq.) and BOP (1770 mg; 4.0 mmol; 1.1 eq.) were suspended in MeCN, treated with triethylamine (4 mL; 29 mmol) and stirred for 18h at room temperature; concentrated and purified by chromatographic column on silica gel (elution 50% EtOAc in DCM) to render 527 mg (1.37 mmol; 38 % yield) of compound **424c** which was 90% pure. 1H-NMR (300.07 MHz; DMSO-*d6*) δ (ppm): 8.56 (s, 1H), 7.78 (d, J=7.9 Hz, 2H), 7.43 (d, J = 3.5 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 3.5 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 6.13 (dd, J = 2.6, 8.3 Hz, 1H), 4.33 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). LRMS: calc: 383.4642; found: 384.2 (M+H); 406.2 (M+Na) and 192.6 (M+2H)/2.

Scheme 61



Step 1: Methyl-(5-nitrobenzothiazol-2-yl)-amine (**456a**)

[0381] A mixture of 2-fluoro-5-nitroaniline (861 mg; 5.52 mmol; 1.02 eq); Im_2CS (960.3 mg; 5.39 mmol) and dry K_2CO_3 (1.45g) was

suspended in dry DME (10 mL) and stirred under nitrogen for 90 min at room temperature. The yellow suspension was made fluid by diluting with DME (10 mL) followed by addition of 40% $MeNH_2$ in water (4.0 mL; 46.5 mmol; 8.6 eq). The system was heated up to 65C and stirred at this temperature for 3.5 h, cooled down, diluted with ethyl acetate and washed with saturated NaCl (X2). After conventional work-up procedures, the dark crude mixture was purified through chromatographic column on silica gel (elution 50% EtOAc in hexane, then 5% MeOH in DCM), to afford 836.8 mg (4.0 mmol; 72% yield) of compound **456a**.

Step 2: *N*-Methyl-benzothiazole-2,5-diamine (**456b**)

[0382] A mixture of nitro compound **456a** (593 mg; 2.83 mmol); $SnCl_2$ (4.02 g; 20.8 mmol; 7.35 eq) and NH_4OAc (4.5g) was suspended in THF:MeOH:H_2O = 1:1:1 (60 mL) and stirred at 70°C for 2 h, cooled down, diluted with ethyl acetate and successively washed with saturated $NaHCO_3$ and brine; dried ($MgSO_4$) filtered and concentrated. The residue (443 mg; 2.43 mmol; 87%) showed consistent spectrum and suitable purity degree for synthetic purposes, therefore was submitted to the next step without further purification.

Step 3: 4-[(2-Methylaminobenzothiazol-5-Ylamino)-Methyl]-Benzoic Acid (**456c**)

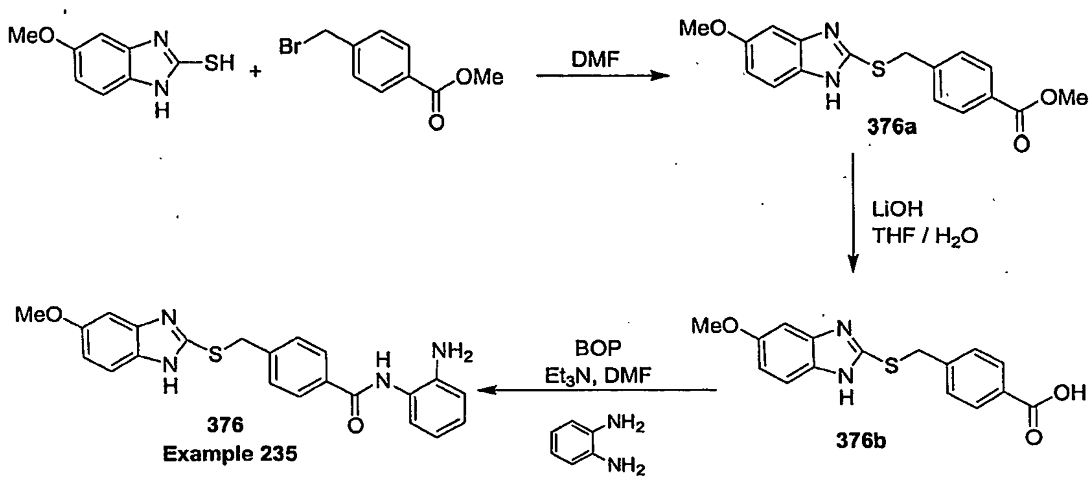
[0383] A solution of aniline **456b** (509 mg; 2.8 mmol); 4-formylbenzoic acid (426 mg; 2.8 mmol) and Bu_2SnCl_2 (198 mg; 0.65 mmol; 23% mol) in DME (14 mL) was stirred at room temperature for 3 min and treated with neat $PhSiH_3$ (0.6 mL; 4.7 mmol; 1.7 mmol) and allowed to react for 18h. After quenching the excess of silane with MeOH, the mixture was concentrated and purified by chromatographic column on silica gel (elution 5% MeOH in DCM) to give 729 mg (2.54 mmol; 91% yield) of acid **456c**.

Step 4: *N*-(2-Aminophenyl)-4-[(2-methylaminobenzothiazol-5-ylamino)-methyl]-benzamide (**456**)

[0384] A mixture of acid **456c** (729 mg; 2.54 mmol), 1,2-phenylenediamine (376 mg; 3.47 mmol; 1.36 eq) and BOP (1.43 g; 3.23 mmol; 1.27 eq) was dissolved in acetonitrile (15 mL), treated with triethylamine (3mL) and stirred overnight. The reaction mixture was quenched with methanol, concentrated and purified by chromatographic column on silica gel (40% EtOAc in DCM) and the obtained material crystallized from DCM to give 358 mg (0.88 mmol; 35 % yield) of pure

compound **456**. ^{1}H-NMR (300 MHz; DMSO-*d6*) δ (ppm): 9.57 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 4.8 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.76 4.87 (bs, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.13 (dd, J = 1.8, 8.3 Hz, 1H), 6.27 (t, J = 5.7 Hz, 1H), 4.87 (bs, 2H), 4.36 (d, J = 5.7 Hz, 2H), 2.85 (d, J = 4.8 Hz, 3H). LRMS: calc: 403.5008, found: 404.2 (M+NH) and 202.6 (M+2H)/2.

Scheme 62



Example 235

Step 1: Methyl-4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoate (**376a**)

[0385] To a solution 5-methoxy-2-thiobenzimidazole (2.00 g, 11.1 mmol of in anhydrous DMF (40 ml) was added methy-4-(bromomethyl)-benzoate (2.54 g, 11.1 mmol). The reaction mixture was stirred 16 h at room temperature. The DMF was evaporated and the residue was triturated in ethyl acetate during 30 min and then filtered and dried. The desired compound was isolated as the HBr salt: 98% yield, (4.44 g). ^{1}H NMR: (DMSO) δ (ppm): 7.90 (d, J = 8.8 Hz, 2H), 7.56-7.52 (m, 3H), 7.09 (d, J = 2.2 Hz, 1H), 7.01 (dd, J = 8.8 , 2.2 Hz, 1H), 4.73 (s, 2H), 3.82 (s, 6H). MS: (calc.) 328.1, (obt.), 329.2 (MH)+.

Step 2: 4-(5-Methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid (**376b**)

[0386] A solution of LiOH.H2O (1.02 g, 24.4 mmol) in water (15 ml) was added to a suspension of **376a** (3.99 g, 9.75 mmol of in THF (10

ml). The reaction mixture was stirred 16 h at room temperature. The reaction mixture was acidified with a solution of HCl 1 M to pH 4. The desired product was triturated 20 min. at 0°C and then filtered and dried. Compound **376b** was obtained as a white powder (100% yield, 3.05 g). ^{1}H NMR: (DMSO) δ (ppm): 12.85 (bs, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.8 , 2.2 Hz, 1H), 4.60 (s, 2H), 3.82 (s, 3 H). MS: (calc.) 314.1, (obt.), 315.1 (MH)+.

Step 3: *N*-(2-Amino-phenyl)-4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzamide (**376**)

[0387] Following the procedure described in Example 1 step 5 but substituting 4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid 2 for 7 the title compound **376** was obtained as a white powder.: 36% yield (933 mg). ^{1}H NMR: (DMSO) δ (ppm): 12.42 (bs, 1H), 9.57 (bs, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.98-6.93 (m, 2H), 6.77-6.55 (m, 2H), 6.58 (dd, J = 7.3, 7.3 Hz, 1H), 4.87 (s, 2H), 4.59 (s, 2H), 3.77 (s, 3 H). MS: (calc.) 404.1, (obt.), 405.4 (MH)+.

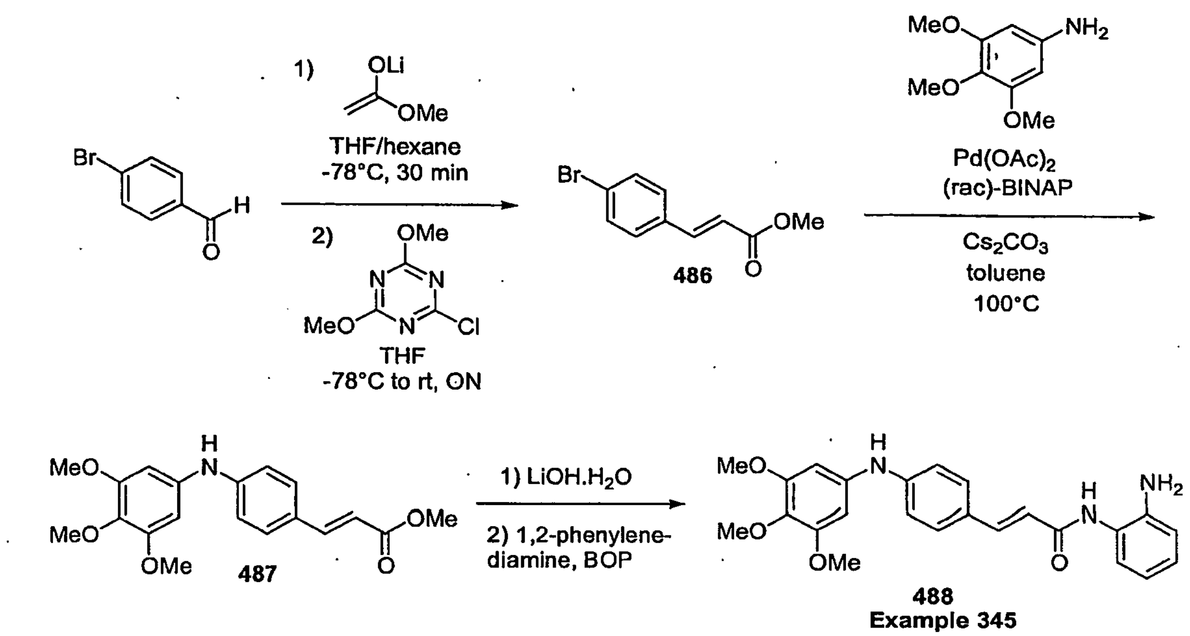
Examples 180-328

[0388] Examples **180** to **327** (compounds **320** - **468**) were prepared using the same procedure as described for compound **126** to **319** in Example **85** to **179** (scheme **11** to **58**).

Examples 329-344

[0389] Examples **329** to **344** (compounds **470** - **485**) were prepared using the same procedure as described for compound **8** to **224** in Example **1** to **143** (scheme **1** to **32**).

Scheme 63



Example 345

Step 1: Methyl 3-(4-bromo-phenyl)-acrylic ester (**486**)

[0390] To a solution of anhydrous *i*-Pr_2NH (758 µl, 5.40 mmol) in anhydrous THF (25 ml) stirred at 0°C under nitrogen , was slowly added a solution of *n*-BuLi (2.22 ml, 5.54 mmol, 2.5 M in hexane). After 30 min, LDA was cooled to -78°C and anhydrous methyl acetate (430 □l, 5.40 mmol) was added dropewise. After 30 min, a solution of 4-bromobenzaldehyde (500 mg, 2.70 mmol) in anhydrous THF (10 ml) was slowly added. After 30 min, a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (569 mg, 3.24 mmol) in anhydrous THF (15 ml) was added. Then, the temperature was allowed to warm up to room temperature overnight. A suspension appeared. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt/hexane: 10/90) to give the title product **486** (394 mg, 1.9 mmol, 61% yield) as a colorless crystalline solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.63 (d, J = 16.2 Hz, 1H), AB system (δ_A = 7.53, δ_B = 7.39, J = 8.4 Hz, 4H), 6.43 (d, J = 15.8 Hz, 1H), 3.82 (s, 3H).

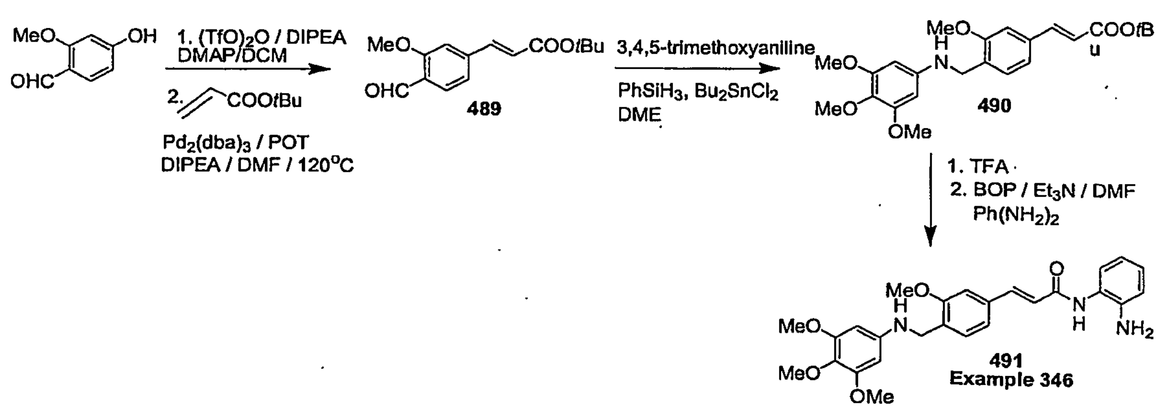
Step 2: Methyl 3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylic ester (**487**)

[0391] A mixture of Cs_2CO_3 (378 mg, 1.16 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), (rac)-BINAP (23 mg, 0.037 mmol), was purged with nitrogen for 10 min. **486** (200 mg, 0.83 mmol), 3,4,5-trimethoxyaniline (182 mg, 0.99 mmol), and anhydrous toluene (5 ml) were added, respectively. The reaction mixture was heated to 100°C under nitrogen for 24 h. Then, it was allowed to cool to room temperature, diluted with AcOEt, and successively washed with a saturated aqueous solution $NaHCO_3$, H_2O, *sat.* NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the title compound **487** (280 mg, 0.82 mmol, 98% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (d, J = 16.2 Hz, 1H), 7.43 (bd, J = 7.9 Hz, 2H), 7.12-6.86 (m, 2H), 6.60-6.20 (m, 3H, included at 6.29, d, J = 15.8 Hz), 3.84 (s, 9H), 3.80 (s, 3H)..

Step 3: *N*-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylamide (**488**)

[0392] The title compound **488** was obtained from **487** in 2 steps following the same procedure as Example 1, steps 4 and 5. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.29 (s, 1H), 8.48 (s, 1H), 7.60-7.42 (m, 3H), 7.38 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.94 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 15.8 Hz, 1H), 6.61 (t, J = 7.1 Hz, 1H), 6.47 (s, 2H), 4.97 (s, 2H), 3.79 (s, 6H), 3.66 (s, 3H).

Scheme 64



Example 346

Step 1: 3-(4-Formyl-3-methoxy-phenyl)-acrylic acid tert-butyl ester **489**

[0393] Following the procedure described in Example 53, step 1, but substituting 4-hydroxy-2-methoxy-benzaldehyde for **84**, followed by Example 42, step 2, but substituting the previous compound for **42**, the title compound **489** was obtained in 29% yield. LRMS = calc: 262, found: 263.2 ($M+H^+$).

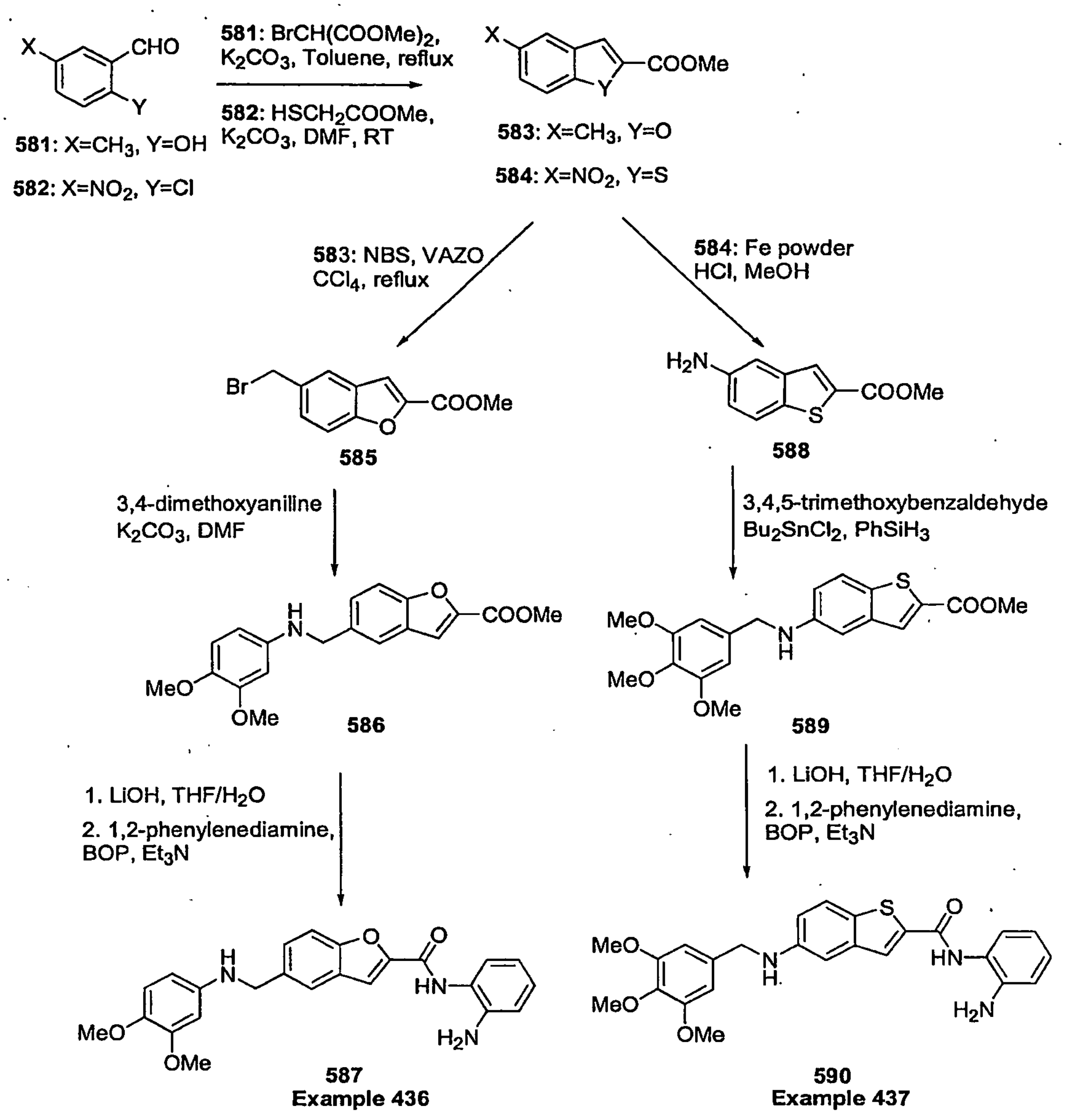
Step 2: 3-{3-Methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylic acid tert-butyl ester **490**

[0394] Following the procedure described in Example 144, step 3, but substituting **489** for 4-formylbenzaldehyde, the title compound **490** was obtained in 69% yield. LRMS = calc: 429, found: 430.5 ($M+H^+$).

Step 3: *N*-(2-Amino-phenyl)-3-{3-methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide **491**

[0395] Following the procedure described in Example 42, step 3, 4, but substituting **490** for **46**, the title compound **491** was obtained in 67% yield. **^{1}H NMR ($CDCl_3$), δ (ppm):** 8.08 (s, 1H), 7.74 (d, J = 15.4 Hz, 1H), 7.30 (m, 1H), 7.06 (m, 3H); 6.80 (m, 3H), 6.70 (d, J = 15.4 Hz, 1H), 5.98 (s, 2H), 4.40 (s, 2H); 4.12 (bs, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.77 (s, 6H).

Scheme 65



Example 436

Step 1: Methyl-5-methyl-benzofuran-2-carboxylate (583)

[0396] A stirring suspension of 5-methylsalicylaldehyde (1.0 mg, 7.5 mmol), K_2CO_3 (1.55 g, 11.0 mmol), and Bu_4NBr (322 mg, 1 mmol) in toluene (30ml) was treated with dimethylbromomalo-nate (1.06 ml, 8.0 mmol). The suspension was heated to reflux with a Dean-Stark trap for 20 h. The brown suspension was cooled to 25°C and concentrated in vacuo. The residue was taken in DCM and filtered. The filtrate was washed with H_2O, 1N NaOH and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude residue was

purified by column chromatography (10% ethyl acetate/hexane) to afford the title compound **583** (600mg, 42% yield). LRMS : 190.2 (Calc.); 191.1 (found).

Step 2: Methyl-5-bromomethyl-benzofuran-2-carboxylate (585)

[0397] A mixture of **583** (500 mg, 2.63 mmol), *N*-bromosuccinimide (561 mg, 3.15 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (Vazo) (63 mg, 0.26 mmol) in 15 ml of CCl_4 was heated overnight under reflux. The mixture was cooled to room temperature, quenched by adding water and extracted with DCM. The organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (30% ethyl acetate/hexane) to afford the title compound **585** (680mg, 96% yield). ^{1}H NMR: ($CDCl_3$) δ (ppm): 7.79 (s, 1H), 7.70-7.52 (m, 3H), 4.69 (s, 2H), 4.06 (s, 3H), 3.72 (s, 2H). LRMS : 268.2 (Calc.); 269.1 (found).

Step 3: Methyl-5-[(3,4-dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylate (586)

[0398] Following the procedure described in Example 47, step 2, but substituting **585** for **63**, the title compound **586** was obtained in 40% yield. LRMS : 341 (Calc.); 342.3 (found).

Step 4: 5-[(3,4-Dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (587)

[0399] Following the procedure described in Example 1, steps 4,5, but substituting **585** for **6**, the title compound **587** was obtained in 29% yield. ^{1}H NMR: (DMSO) δ (ppm): 9.83 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.33 (s, 1H), 6.04 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 5.5 Hz, 1H), 4.93 (s, 2H), 4.31 (d, J = 5.5 Hz, 1H), 2.82 (s, 3H), 2.76 (s, 3H). LRMS : 417.46 (Calc.); 418.4 (found).

Example 437

Step 1: Methyl-5-nitro-benzo[b]thiophene-2-carboxylate (584)

[0400] A stirring suspension of 5-nitro-2-chloro-benzaldehyde (4.0 g, 21.6 mmol) in DMF (40 ml) at 5°C was treated with K_2CO_3 (3.52 g, 25.5 mmol) followed by methylglycolate (1.93 ml, 21.6 mmol). The resulting solution was warmed to 25°C and stirred for 20h. The

solution was then poured into 250ml of ice H_2O and the white precipitate that formed was collected by filtration. Crystallization from EtOAc afforded fine pale orange needles of **584** (3.54 g, 69%). LRMS : 237.0 (Calc.); 238.1 (found). ^{1}H NMR: (DMSO) δ (ppm): 9.00 (d, J = 2.2 Hz, 1H), 8.45 (s, 1H), 8.39-8.30 (m, 2H), 3.93 (s, 3H).

Step 2: Methyl-5-amino-benzo[b]thiophene-2-carboxylate (588)

[0401] A suspension of **584** (3.52 g, 14.8 mmol) in methanol (100 ml) was treated with Fe powder (6.63 g, 118.7 mmol). The resulting suspension was heated to reflux, and 12M HCl (8.5 ml) was slowly added over 15 min. The resulting green dark suspension was refluxed for an additional 3 h, then cooled and concentrated. The residue was taken up in EtOAc and washed with saturated aqueous $NaHCO_3$, then brine, dried over $MgSO_4$, filtered and concentrated to afford (2.57 g, 84%). ^{1}H NMR: (DMSO) δ (ppm): 7.92 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 1.8, 8.4 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H). LRMS : 207.0 (Calc.); 208.1 (found).

Step 3: Methyl-5-(3,4,5-trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylate (589)

[0402] Following the procedure described in Example 144, step 3, but substituting **588** for **226**, the title compound **589** was obtained in 68% yield. (DMSO) δ (ppm): 7.94 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.02-6.99 (m, 2H), 6.73 (s, 2H), 6.41 (t, J = 5.7 Hz, 1H), 4.21 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 6H), 3.62 (s, 3H). LRMS : 387.1 (Calc.); 388.3 (found).

Step 4: 5-(3,4,5-Trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (590)

[0403] Following the procedure described in Example 1, steps 4,5, but substituting **589** for **6**, the title compound **590** was obtained in % yield^{1}H NMR: (DMSO) δ (ppm): 7.79 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.00-6.95 (m, 2H), 6.74 (s, 2H), 4.32 (s, 2H), 3.80 (s, 6H), 3.73 (s, 3H).

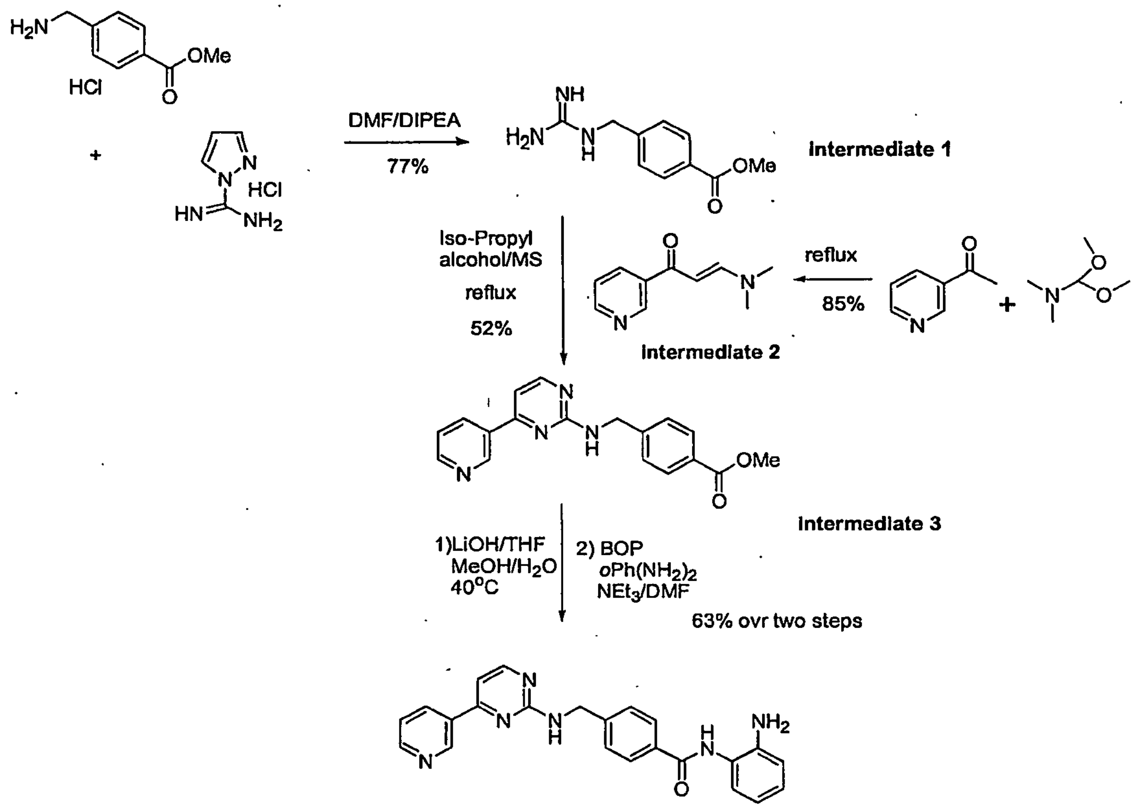
Examples 347-425

[0404] Examples **347** to **425** (compounds **492-570**) were prepared using the same procedure as described for compound **44** to **491** in Example **40** to **346** (scheme **3** to **64**).

Example 426

Synthesis of N-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide

Scheme 66



Step 1: Synthesis of 4-Guanidinomethyl-benzoic acid methyl ester Intermediate 1

[0405] The mixture of 4-Aminomethyl-benzoic acid methyl ester HCl (15.7 g, 77.8 mmol) in DMF (85.6 mL) and DIPEA (29.5 mL, 171.2 mmol) was stirred at rt for 10 min. Pyrazole-1-carboxamidine HCl (12.55 g, 85.6 mmol) was added to the reaction mixture and then stirred at rt for 4 h to give clear solution. The reaction mixture was evaporated to dryness under vacuum. Saturated $NaHCO_3$ solution (35 mL) was added to give nice suspension. The suspension was filtered and the filter

cake was washed with cold water. The mother liquid was evaporated to dryness and then filtered. The two solids were combined and re-suspended over distilled H_2O (50 ml). The filter cake was then washed with minimum quantities of cold H_2O and ether to give 12.32 g white crystalline solid intermediate 1 (77% yield, M+1: 208 on MS).

Step 2: Synthesis of 3-Dimethylamino-1-pyridin-3-yl-propenone Intermediate 2

[0406] 3-Acetyl-pyridine (30.0 g, 247.6 mmol) and DMF dimethyl acetal (65.8 mL, 495.2 mmol) were mixed together and then heated to reflux for 4h. The reaction mixture was evaporated to dryness and then 50 mL diethyl ether was added to give brown suspension. The suspension was filtered to give 36.97 g orange color crystalline product (85% yield, M+1: 177 on MS).

Step 3: Synthesis of 4-[(4-Pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzoic acid methyl ester Intermediate 3

[0407] Intermediate 1 (0.394 g,1.9 mmol) and intermediate 2 (0.402 g, 2.3 mmol) and molecular sieves (0.2 g, 4A, powder, >5 micron) were mixed with isopropyl alcohol (3.8 mL). The reaction mixture was heated to reflux for 5h. MeOH (50 mL) was added and then heated to reflux. The cloudy solution was filtrated over a pad of celite. The mother liquid was evaporated to dryness and the residue was triturated with 3 mL EtOAc. The suspension was filtrated to give 0.317g white crystalline solid Intermediate 3 (52%, M+1: 321 on MS).

Step 4: Synthesis of N-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide

[0408] Intermediate 3 (3.68 g, 11.5 mmol) was mixed with THF (23 mL) ,MeOH (23 mL) and H_2O (11.5 mL) at rt. LiOH (1.06 g, 25.3 mmol) was added to reaction mixture. The resulting reaction mixture was warmed up to 40°C overnight. HCl solution (12.8 mL, 2*N*) was added to adjust pH=3 when the mixture was cooled down to rt. The mixture was evaporated to dryness and then the solid was washed with minimum quantity of H_2O upon filtration. The filter cake was dried over freeze dryer to give 3.44 g acid of the title compound (95%, M+1: 307 on MS).

[0409] Acid (3.39g, 11.1 mmol) of the title compound, BOP (5.679g, 12.84 mmol) and *o*-$Ph(NH_2)_2$ (2.314 g, 21.4 mmol) were dissolved in the mixture of DMF (107 mL) and Et_3N (2.98 mL, 21.4 mmol). The reaction

mixture was stirred at rt for 5h and then evaporated to dryness. The residue was purified by flash column (pure EtOAc to 5% MeOH/EtOAc) and then interested fractions were concentrated. The final product was triturated with EtOAc to give 2.80 g of title product (66%, MS+1: 397 on MS). ^{1}H NMR (400 MHz, DMSO-D$_6$) δ (ppm): 9.57 (s, 1H), 9.22 (s,1H), 8.66 (d, J= 3.5 Hz, 1H), 8.39 (d, J= 5.1 Hz, 2H), 8.00 (t, J = 6.5 Hz, 1H), 7.90 (d, J= 8.2Hz, 2H), 7.50 (m, 3H), 7.25 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 6.94 (dd, J = 7.0, 7.8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.57 (dd, J = 7.0, 7.8 Hz, 1H), 4.86 (s, 2H), 4.64 (d, J = 5.9 Hz, 2H).

Assay Example 1

Inhibition of Histone Deacetylase Enzymatic Activity

1. Human HDAC-1

[0410] HDAC inhibitors were screened against a cloned recombinant human HDAC-1 enzyme expressed and purified from a Baculovirus insect cell expression system. For deacetylase assays, 20,000 cpm of the [^{3}H]-metabolically labeled acetylated histone substrate (M. Yoshida *et al., J. Biol. Chem.* **265(28):** 17174-17179 (1990)) was incubated with 30 µg of the cloned recombinant hHDAC-1 for 10 minutes at 37 °C. The reaction was stopped by adding acetic acid (0.04 M, final concentration) and HCl (250 mM, final concentration). The mixture was extracted with ethyl acetate and the released [^{3}H]-acetic acid was quantified by scintillation counting. For inhibition studies, the enzyme was preincubated with compounds at 4 °C for 30 minutes prior to initiation of the enzymatic assay. IC_{50} values for HDAC enzyme inhibitors were determined by performing dose response curves with individual compounds and determining the concentration of inhibitor producing fifty percent of the maximal inhibition. IC_{50} values for representative compounds are presented in the third column of Table 5.

2. MTT Assay

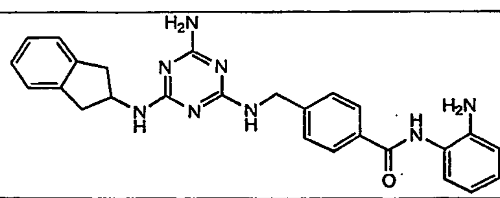
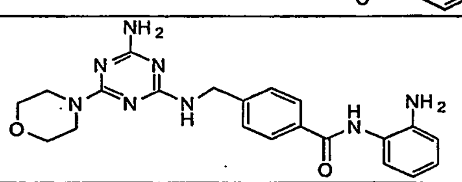
[0411] HCT116 cells (2000/well) were plated into 96-well tissue culture plates one day before compound treatment. Compounds at various concentrations were added to the cells. The cells were incubated for 72 hours at 37°C in 5% CO_2 incubator. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide, Sigma) was added at a final concentration of 0.5 mg/ml and incubated with the cells for 4 hours before one volume of solubilization buffer (50% N,N-

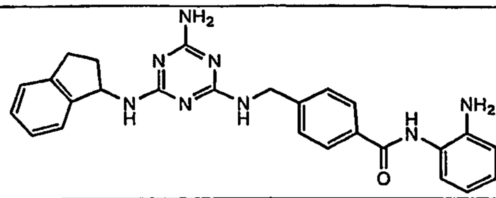
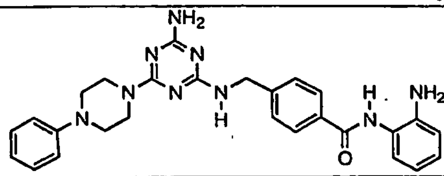
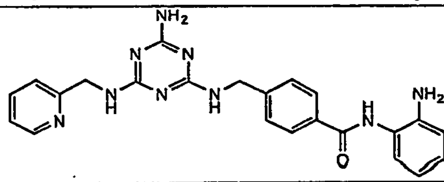
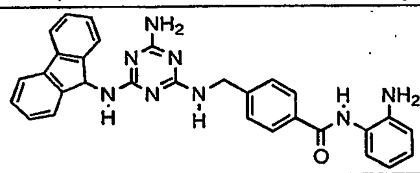
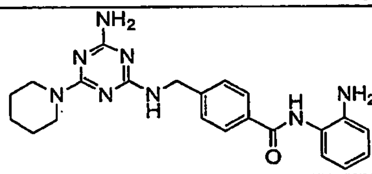
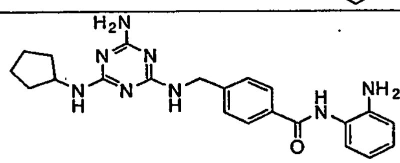
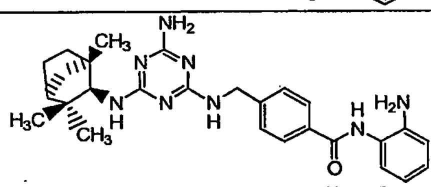
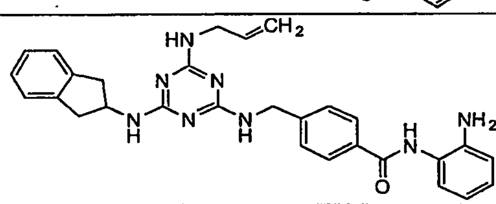
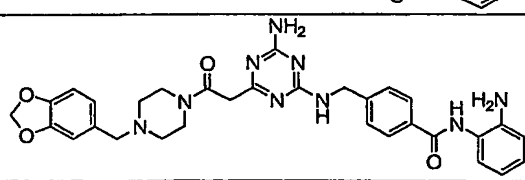
dimethylformamide, 20% SDS, pH 4.7) was added onto the cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM using an MR700 plate reader (Dynatech Laboratories Inc.). OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration which reduces cell numbers to 50% of that of solvent treated cells is determined as MTT IC_{50}. IC_{50} values for representative compounds are presented in the fourth column of Table 5.

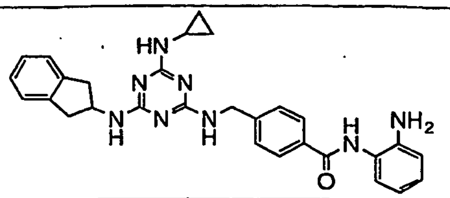
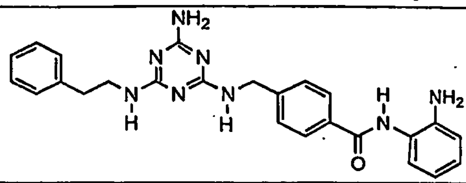
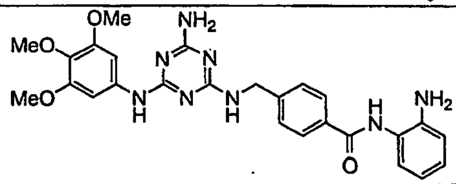
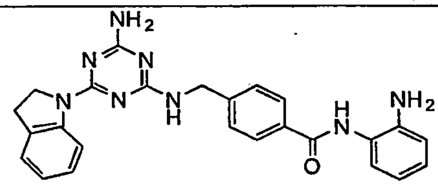
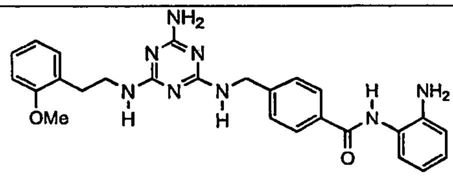
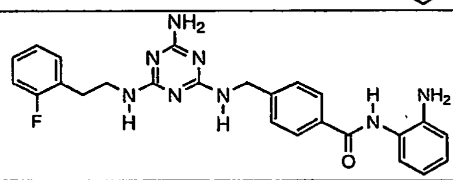
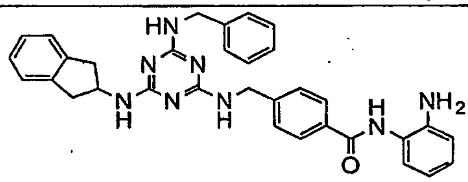
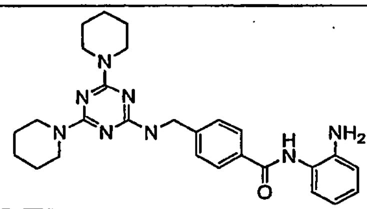
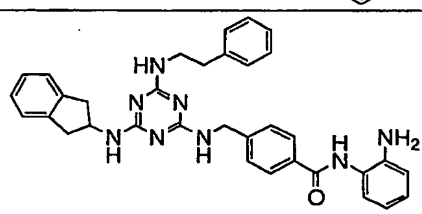
3. <u>Histone H4 acetylation in whole cells by immunoblots</u>

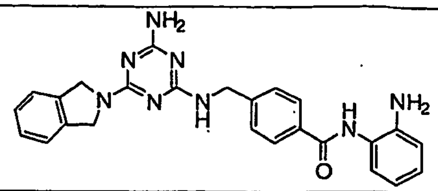
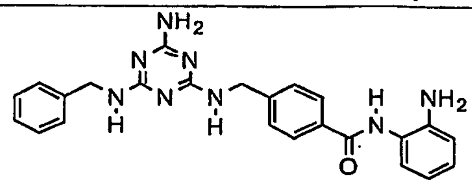
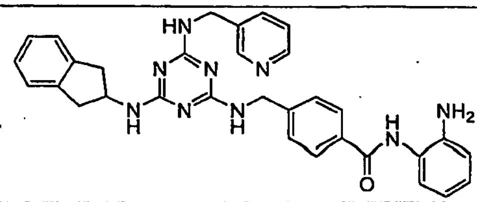
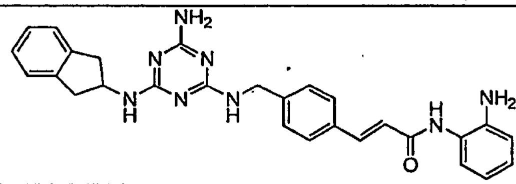
[0412] T24 human bladder cancer cells growing in culture were incubated with HDAC inhibitors for 16 h. Histones were extracted from the cells after the culture period as described by M. Yoshida *et al.* (*J. Biol. Chem.* **265(28)**: 17174-17179 (1990)). 20 g of total histone protein was loaded onto SDS/PAGE and transferred to nitrocellulose membranes. Membranes were probed with polyclonal antibodies specific for acetylated histone H-4 (Upstate Biotech Inc.), followed by horse radish peroxidase conjugated secondary antibodies (Sigma). Enhanced Chemiluminescence (ECL) (Amersham) detection was performed using Kodak films (Eastman Kodak). Acetylated H-4 signal was quantified by densitometry. Representative data are presented in the fifth column of Table 5. Data are presented as the concentration effective for reducing the acetylated H-4 signal by 50% (EC_{50}).

Table 5a: Inhibition of Histone Deacetylase

Cpd	Structure	HumanHDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4Ac (T24) EC_{50} (μM)
8		0.4	0.5	1
9		2	0.7	5

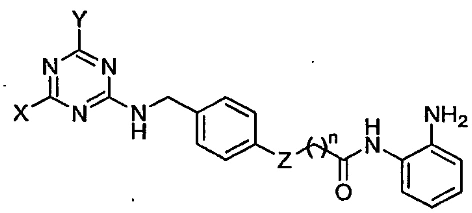
Cpd	Structure	HumanHDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4Ac (T24) EC_{50} (μM)
10		2	0.6	1
11		2	0.6	2
12		2	2	5
14		0.3	1	5
15		0.5	0.2	3
16		1	0.4	1
17		0.9	1	2
18		0.8	0.6	3
18b		0.6	5	10

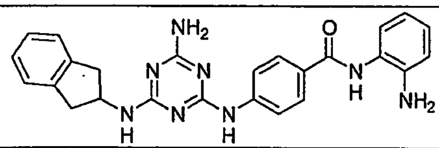
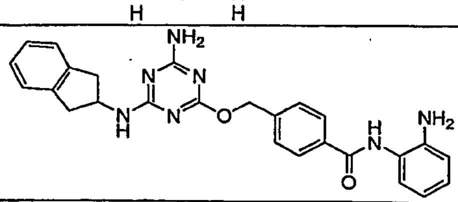
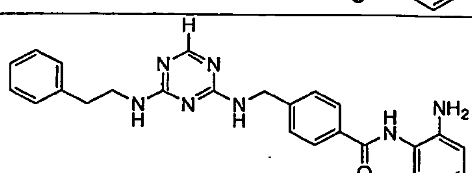
Cpd	Structure	HumanHDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4Ac (T24) EC_{50} (μM)
19		0.9	1	1
20		0.5	0.3	1
21		4	4	25
22		3	0.8	1
23		2	0.7	1
24		3	0.6	1
25		0.8	0.3	5
26		0.5	2	na
27		0.4	2	na

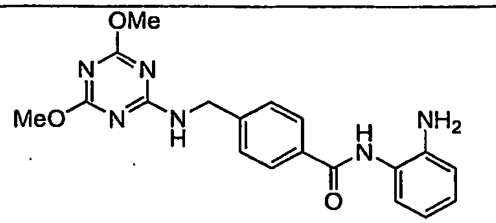
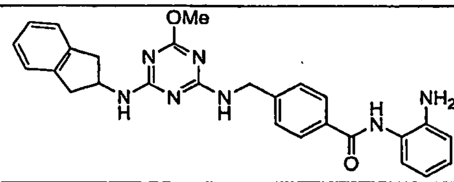
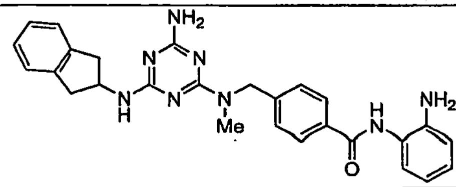
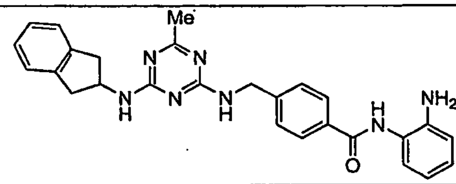
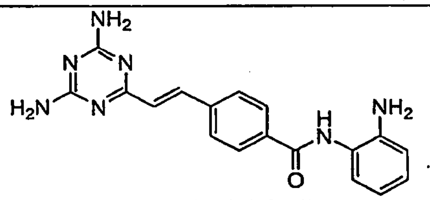
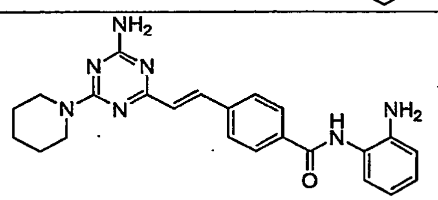
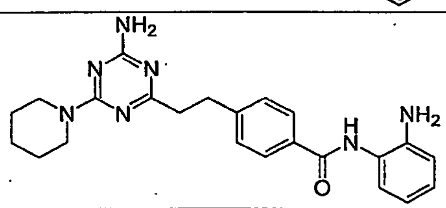
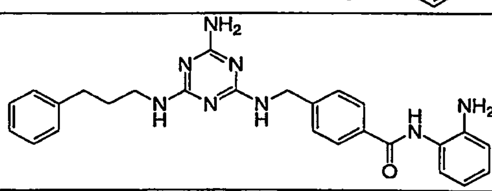
Cpd	Structure	HumanHDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4Ac (T24) EC_{50} (μM)
28		2	0.5	1
29		2	2	1
30		1	3	1
83		3	5	5

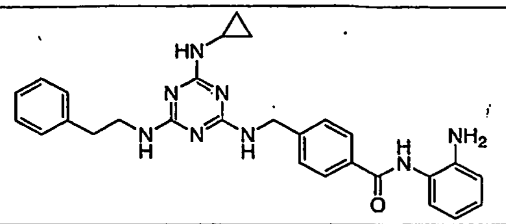
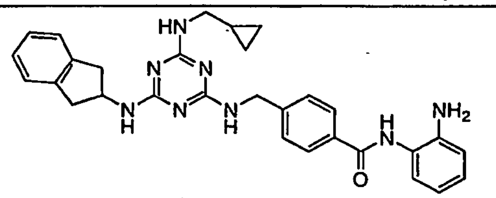
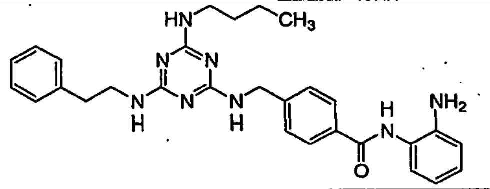
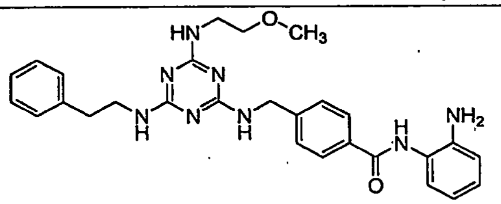
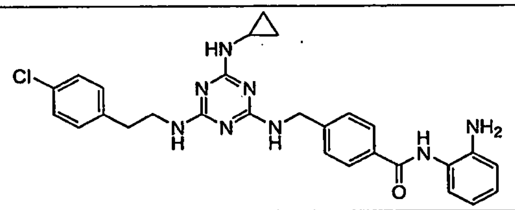
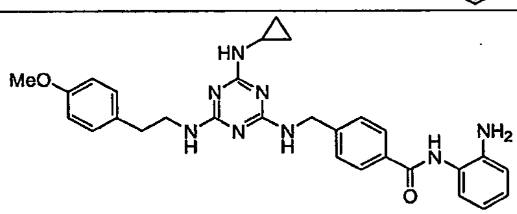
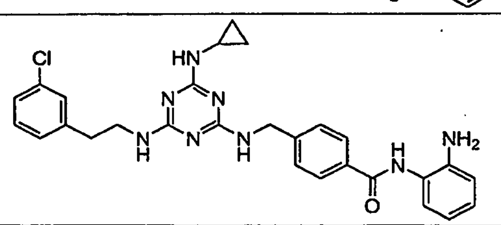
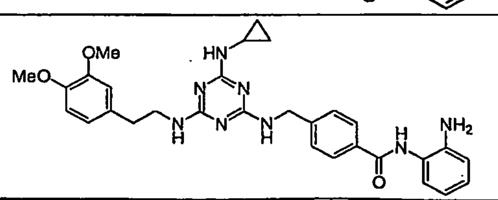
(na = not available; 99 = >25 μM)

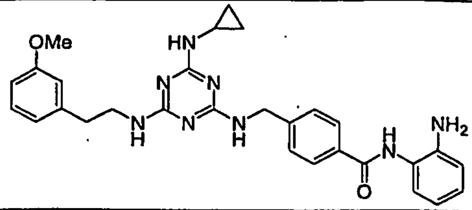
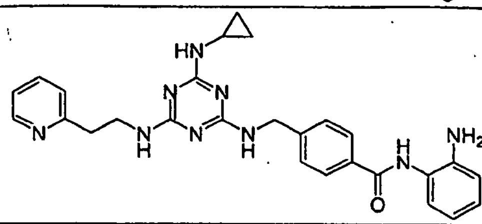
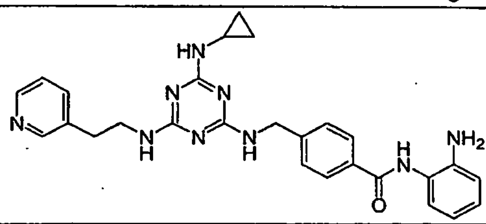
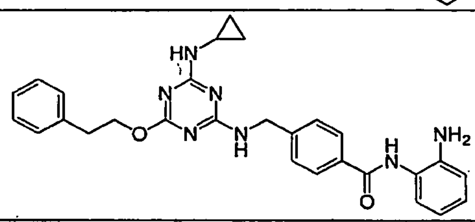
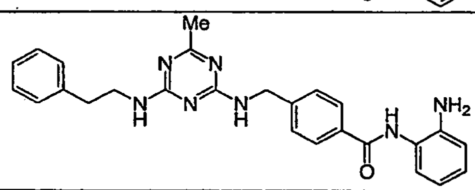
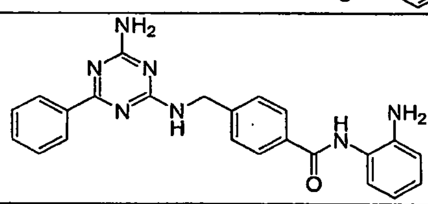
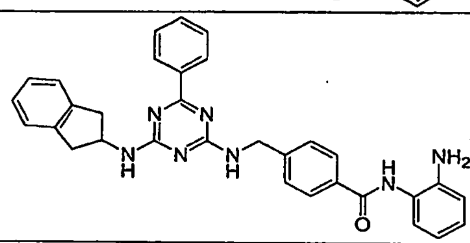
Table 5b



Ex	Cpd	Structure	Human HDAC-1 IC_{50}(μM)	MTT(HCT116) IC_{50}(μM)	H4Ac(T24) EC_{50}(μM)
135	204		4	na	5
136	207		0.4	0.6	2
137	210		3	0.9	1

Ex	Cpd	Structure	Human HDAC-1 $IC_{50}(\mu M)$	MTT(HCT116) $IC_{50}(\mu M)$	H4Ac(T24) $EC_{50}(\mu M)$
138	212		3	1	1
139	214		3	0.9	1
140	216		0.5	0.4	2
141	218		0.1	0.5	na
142	220		7	6	na
143a	223		11	2	na
143b	224		5	3	na
329	470		2	0.7	3

Ex	Cpd	Structure	Human HDAC-1 $IC_{50}(\mu M)$	MTT(HCT116) $IC_{50}(\mu M)$	H4Ac(T24) $EC_{50}(\mu M)$
330	471		0.4	1	3
331	472		3	1	1
332	473		4	3	na
333	474		3	1	1
334	475		0.6	2	na
335	476		2	1	2
336	477		1	0.7	na
337	478		3	0.7	na

Ex	Cpd	Structure	Human HDAC-1 $IC_{50}(\mu M)$	MTT(HCT116) $IC_{50}(\mu M)$	H4Ac(T24) $EC_{50}(\mu M)$
338	479		0.4	0.6	na
339	480		0.8	0.5	na
340	481		6	0.7	na
341	482		0.1	0.7	na
342	483		4	na	na
343	484		2	0.3	na
344	485		0.4	3	na

(na=nonavailable)

Table 5c

Cpd	Structure	HumanHDAC-1 $IC_{50}(\mu M)$	MTT(HCT116) $IC_{50}(\mu M)$	H4Ac(T24) $EC_{50}(\mu M)$

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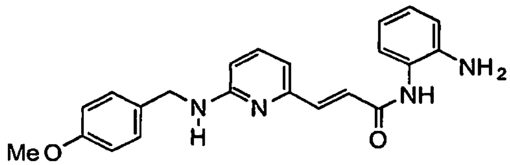
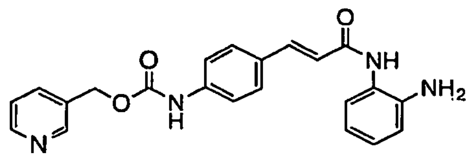
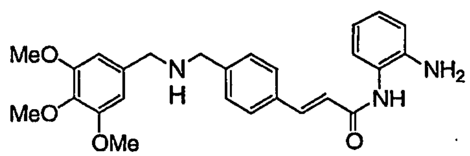
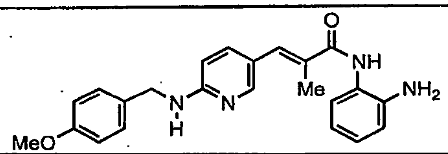
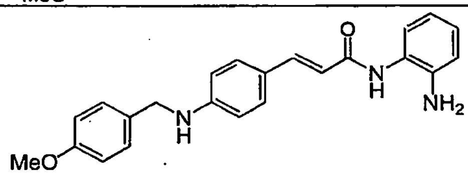
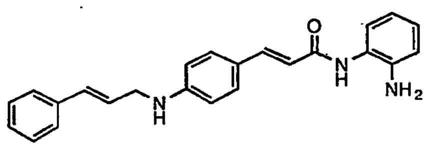
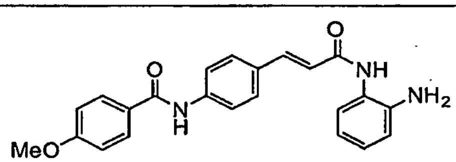
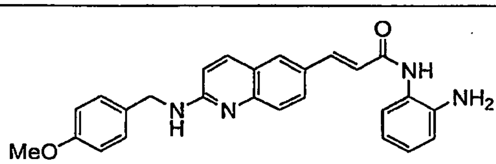
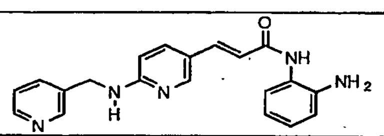
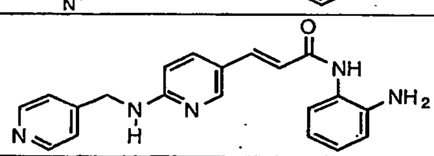
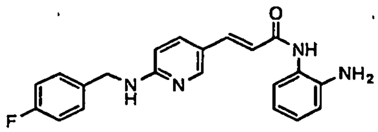
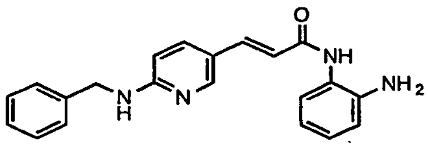
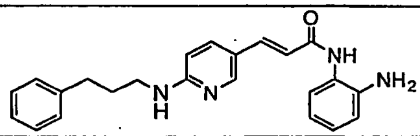
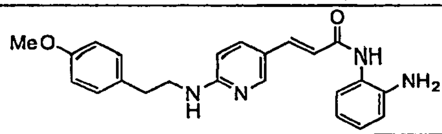
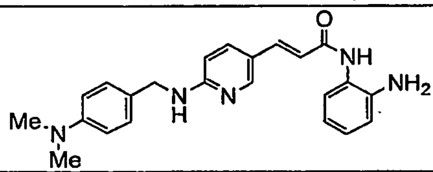
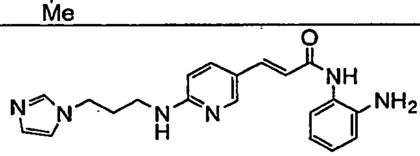
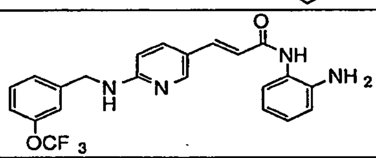
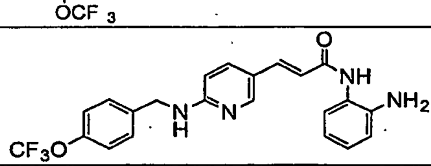
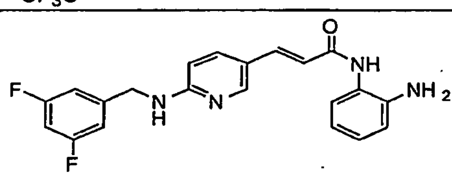
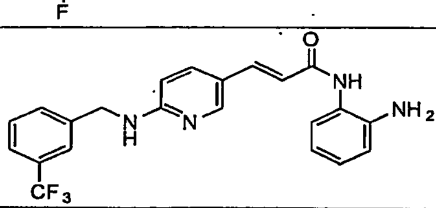
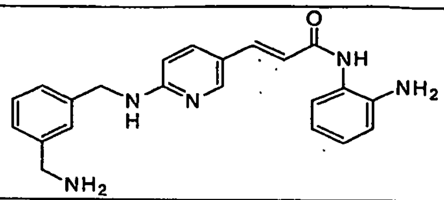
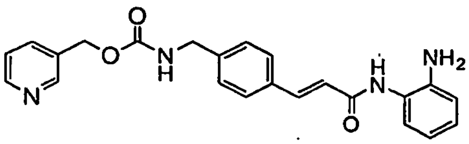
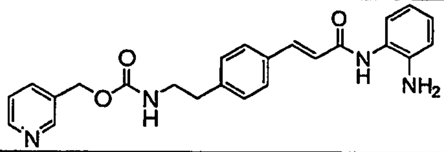
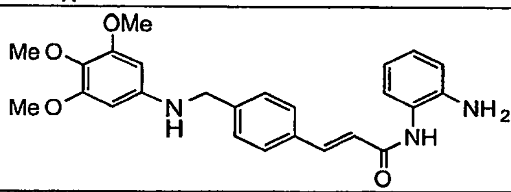
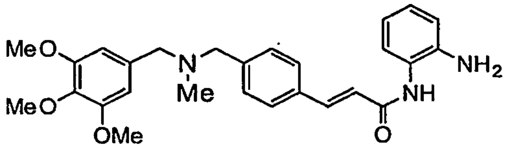
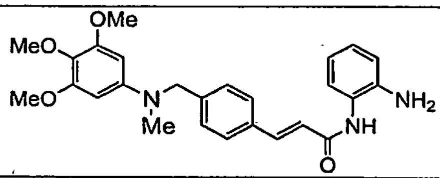
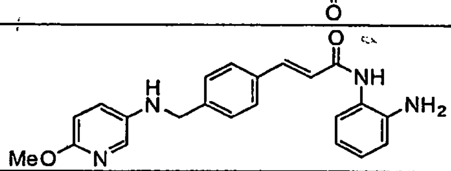
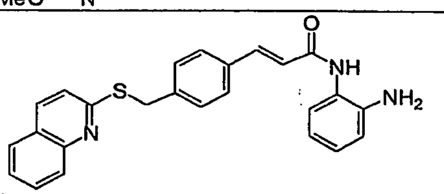
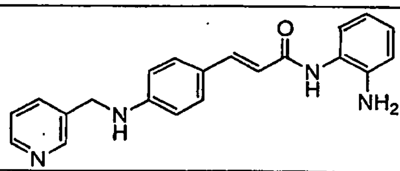
Cpd	Structure	HumanHDAC-1 IC_{50}(μM)	MTT(HCT116) IC_{50}(μM)	H4Ac(T24) EC_{50}(μM)
51		22	4	na
55b		3	8	3
59		12	22	na
61b		7	12	na
65		4	37	na
71		10	44	na
72		16	21	na
88		na	>39	na
90		10	5	5
91		4	7	5

Cpd	Structure	HumanHDAC-1 IC_{50}(μM)	MTT(HCT116) IC_{50}(μM)	H4Ac(T24) EC_{50}(μM)
92		5	2	3
93		3	1	5
94		3	2	5
95		3	2	10
96		4	3	25
97		10	12	na
98		0.4	2	15
99		2	5	10
100		4	3	5
101		3	0.9	5

Cpd	Structure	HumanHDAC-1 $IC_{50}(\mu M)$	MTT(HCT116) $IC_{50}(\mu M)$	H4Ac(T24) $EC_{50}(\mu M)$
102		20	6	na
104		10	9	5
105		16	14	na
106		2	2	1
107		15	17	na
108		3	5	5
109		5	8	15
110		3	999	na
111		10	2	99

SUBSTITUTE SHEET (RULE 26)

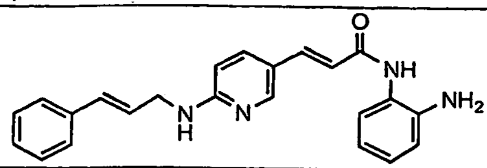
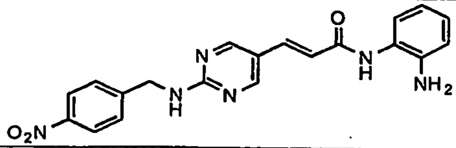
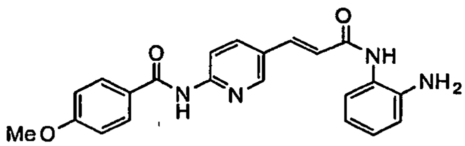
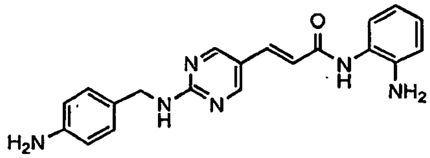
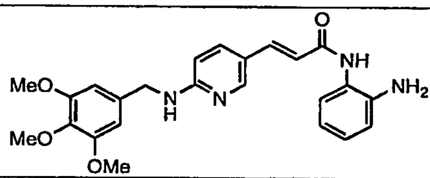
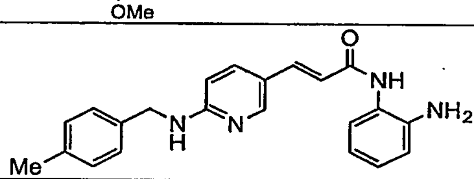
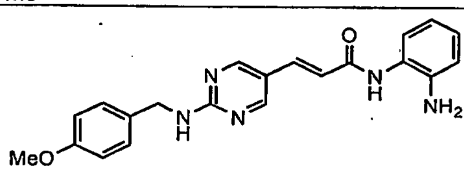
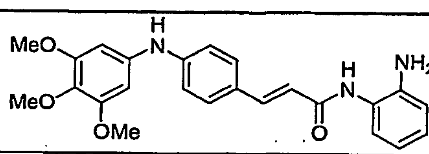
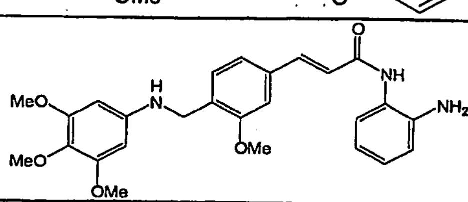
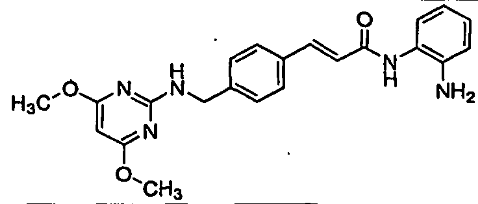
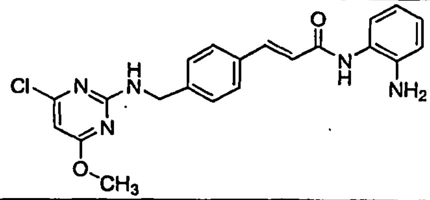
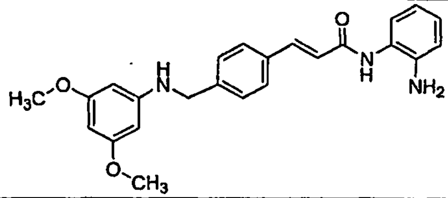
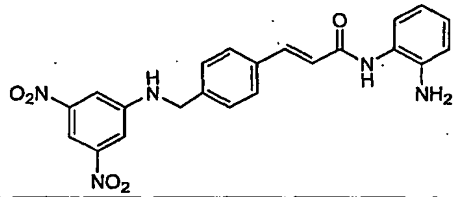
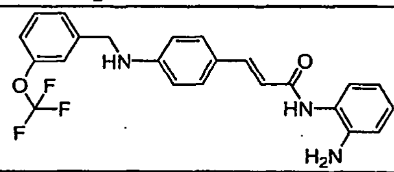
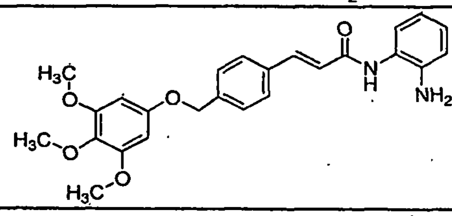
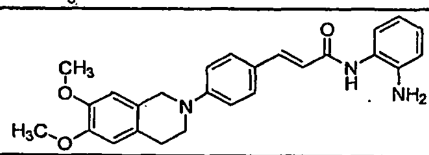
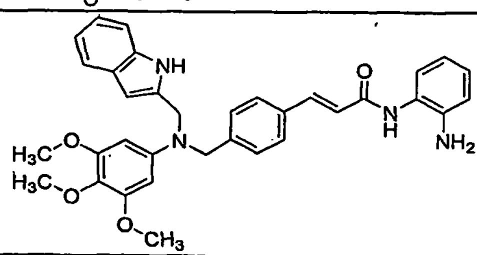
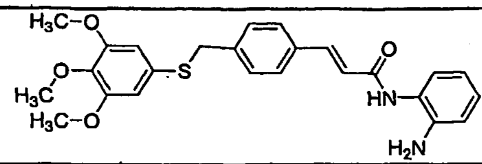
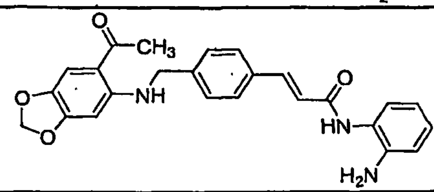
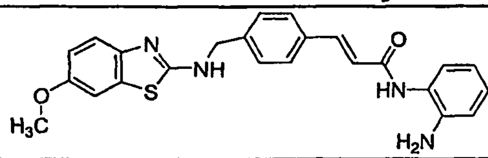
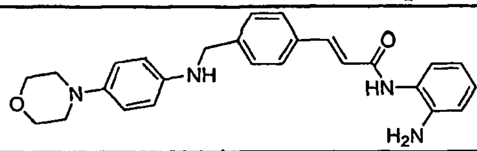
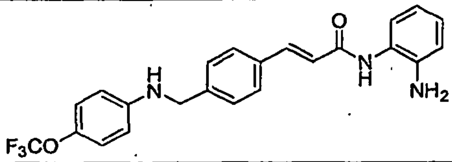
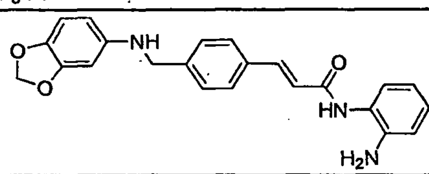
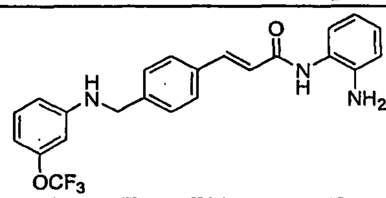
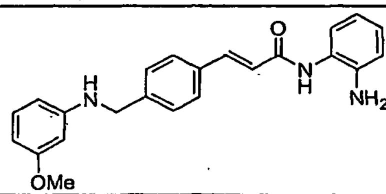
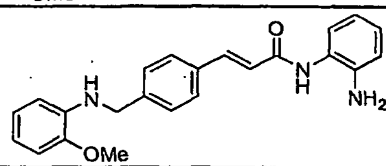
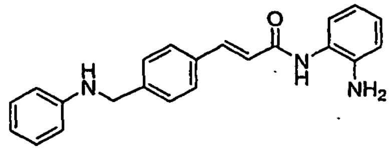
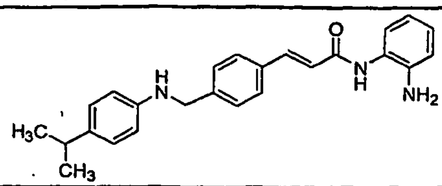
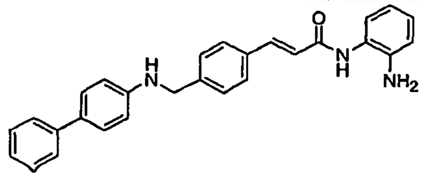
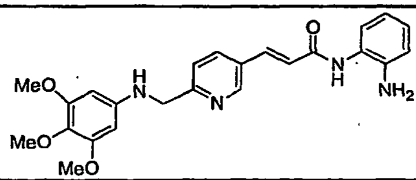
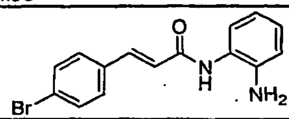
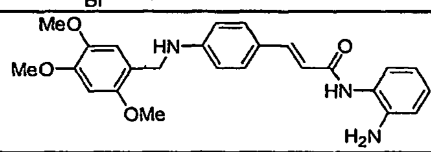
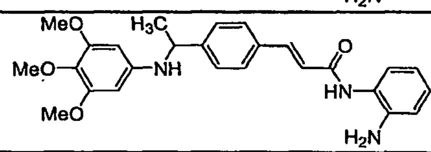
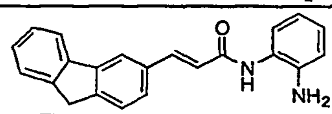
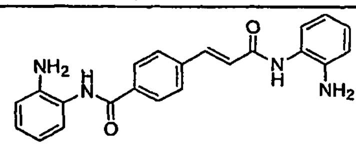
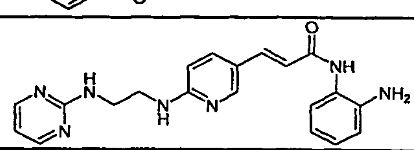
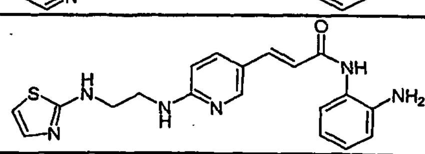
Cpd	Structure	HumanHDAC-1 IC_{50}(μM)	MTT(HCT116) IC_{50}(μM)	H4Ac(T24) EC_{50}(μM)
112		2	5	5
113			0.3	5
114		25	0.5	99
115		15	9	na
116		4	2	5
117		7	3	na
118		11	8	na

Table 5d

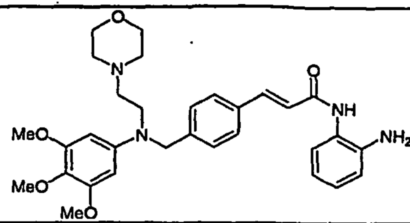
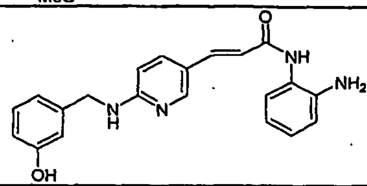
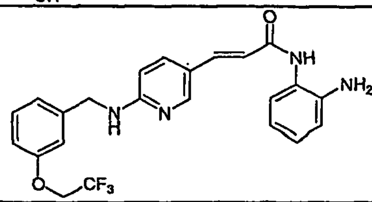
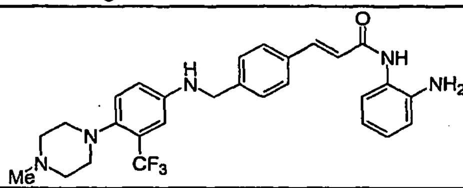
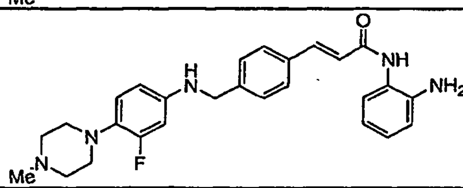
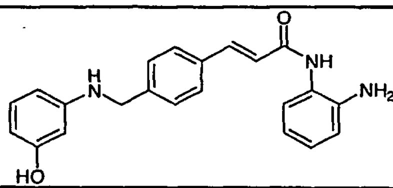
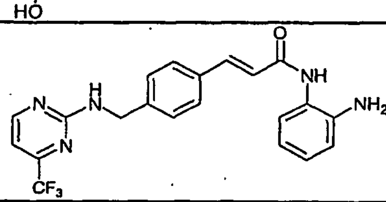
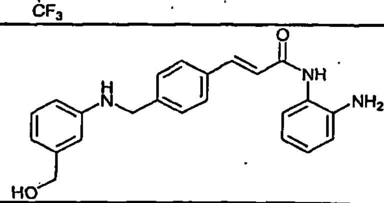
Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
338	481		22	10	-
339	484		20	12	-

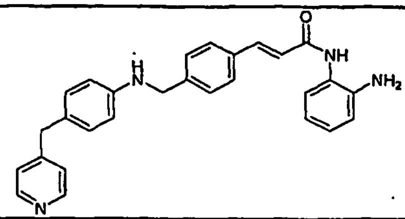
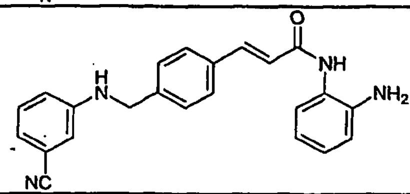
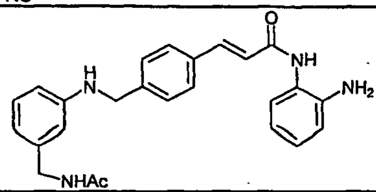
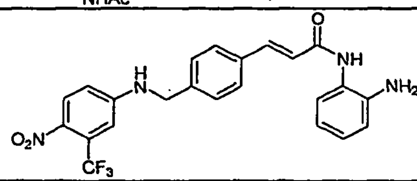
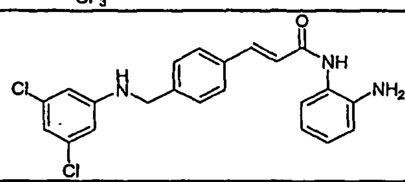
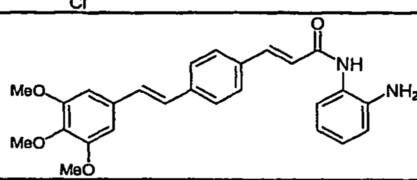
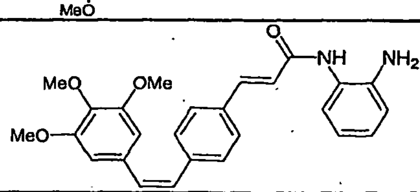
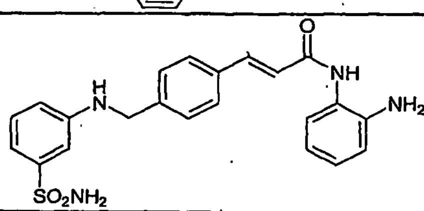
Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
347	492		4	9	10
348	493		4	5	-
349	494		3	4	-
350	495		4	7	-
351	496		8	13	-
352	497		15	6	-
353	498		>25	-	-
354	499		>25	2	>25

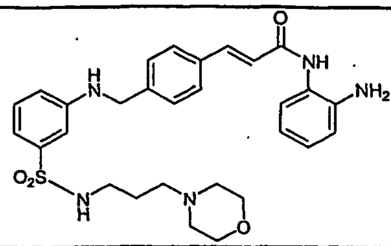
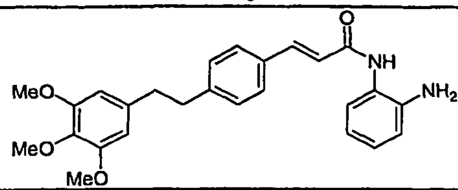
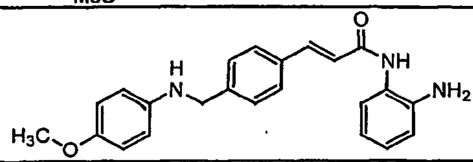
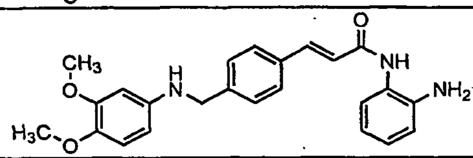
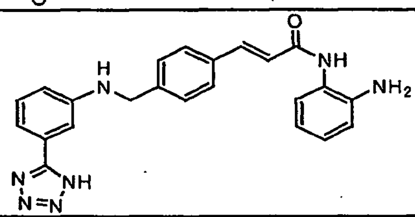
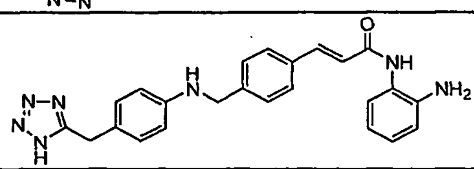
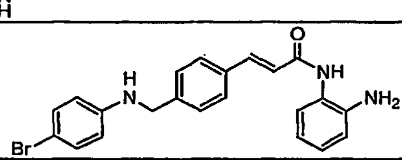
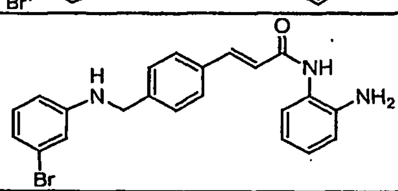
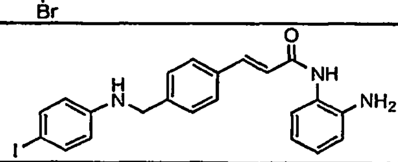
Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
355	500		23	37	-
356	501		4	10	-
357	502		3	>25	-
358	503		5	>25	-
359	504		5	>25	-
360	505		3	6	-
361	506		15	11	-
362	507		17	10	-
363	508		22	11	-

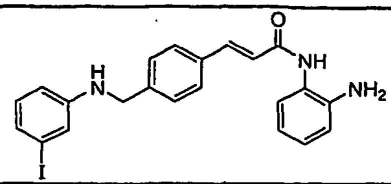
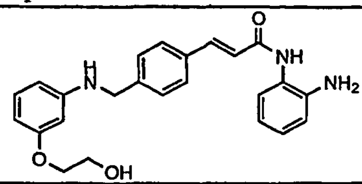
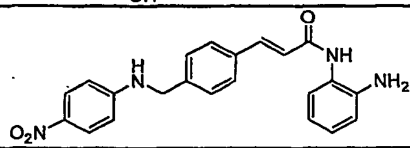
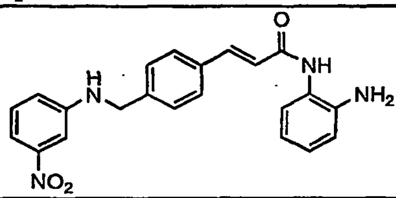
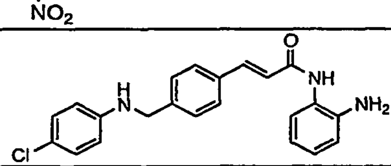
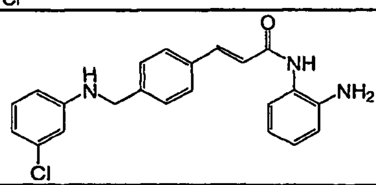
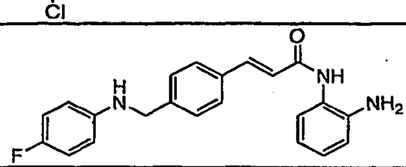
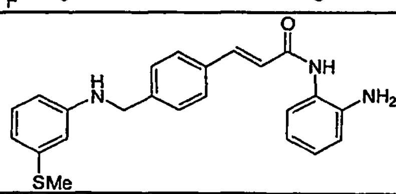
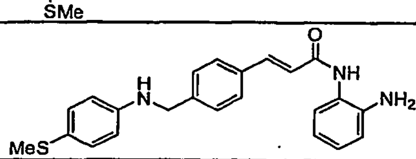
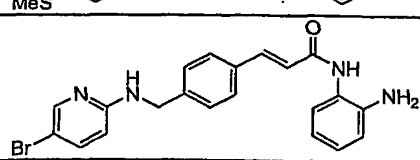
Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
364	509		17	11	-
365	510		6	5	-
366	511		4	>25	-
367	512		3	3	5
371	516		15	15	-
372	517		6	5	-
373	518		4	2	5
374	519		99	6	-
375	520		5	3	-
376	521		5	2	10
377	522		17	30	-

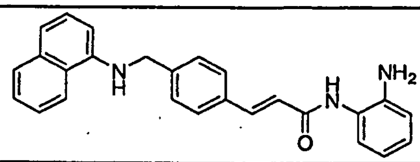
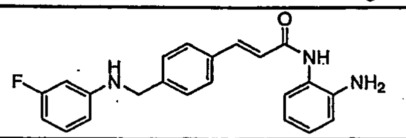
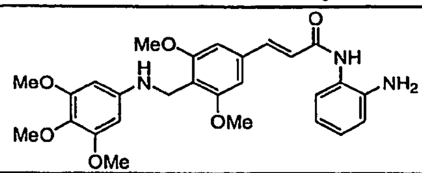
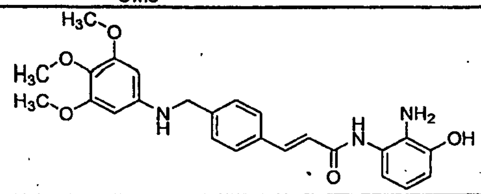
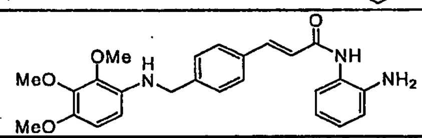
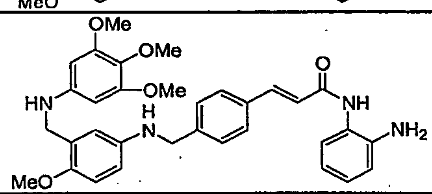
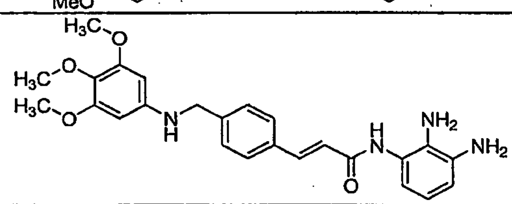
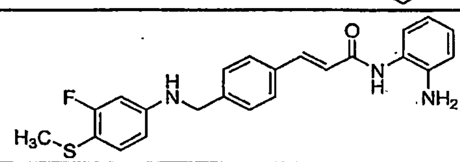
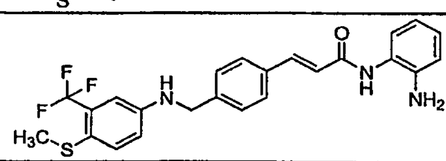
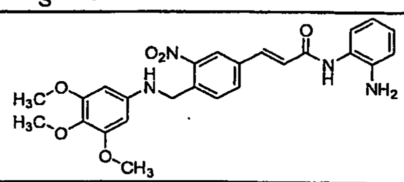
SUBSTITUTE SHEET (RULE 26)

Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
378	523		8	6	10
379	524		3	2	3
380	525		3	4	5
381	526		2	0.8	1
382	527		4	3	-
383	528		20	32	-
384	529		5	17	-
385	530		8	9	-

Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
386	531		3	2	20
387	532		3	5	-
388	533		5	11	-
389	534		3	5	-
390	535		4	6	-
391	536		18	9	-
392	537		11	2	>25
393	538		4	12	-

Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
394	539		2	10	-
395	540		10	10	-
396	541		4	12	-
397	542		2	5	4
398	543		15	>25	-
399	544		17	45	-
400	545		2	12	-
401	546		3	10	-
402	547		4	8	-

Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
403	548		3	9	-
404	549		4	19	-
405	550		4	15	-
406	551		24	9	-
407	552		4	22	-
408	553		4	12	-
409	554		15	12	-
410	555		14	7	-
411	556		1	0.4	15
412	557		4	6	-

Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
413	558		7	10	-
414	559		4	11	-
415	560		21	6	-
416	561		>25	>25	-
417	562		5	5	-
418	563		24	6	-
419	564		>25	>25	-
420	565		5	17	-
421	566		3	16	-
422	567		13	3	-

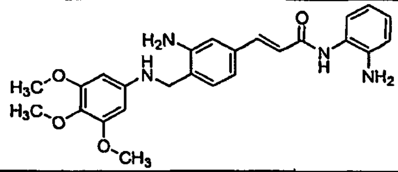
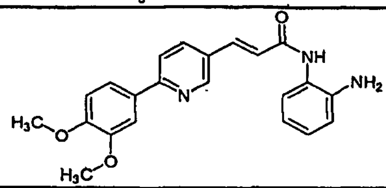
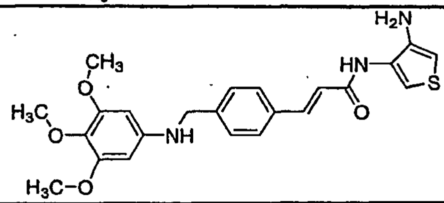
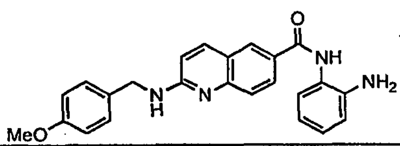
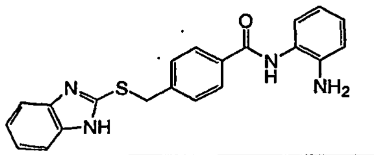
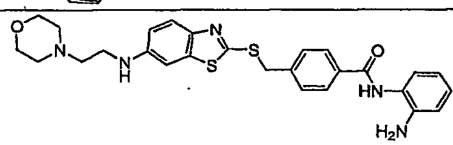
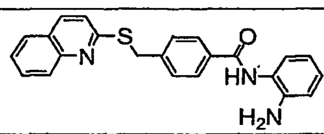
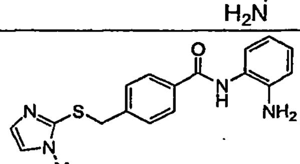
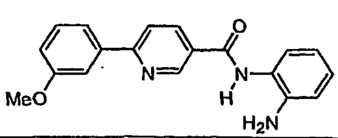
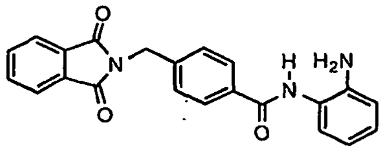
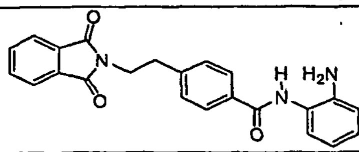
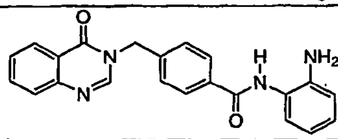
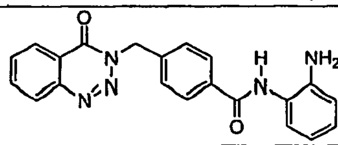
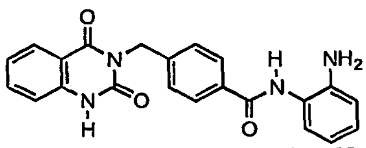
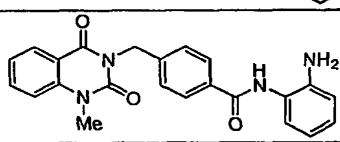
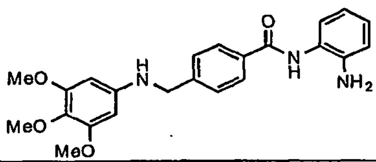
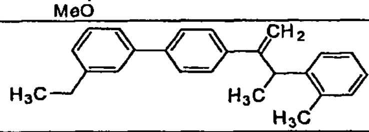
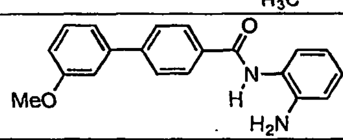
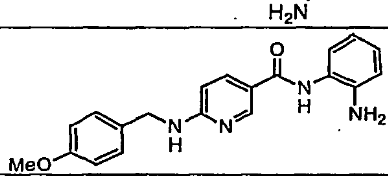
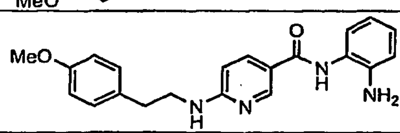
Ex.	Cpd	Structure	HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4Ac (T24) EC50 (μM)
423	568		>25	39	-
424	569		18	6	-
425	570		6	0.6	2

Table 5e

Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
87		2	1	5
126		0.3	0.2	1
128		1	0.3	5
131		0.3	0.9	2
139		3	3	5
141		7	10	na

Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
149		1	5	5
152		0.3	11	na
154		0.3	0.4	<1
155		0.4	0.4	1
157		2	0.6	1
158		0.4	0.2	1
164		3	2	3
165		9	4	25
166		2	5	5
167		4	0.5	2
168		3	0.8	2

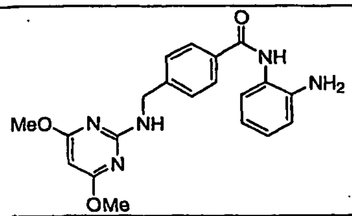
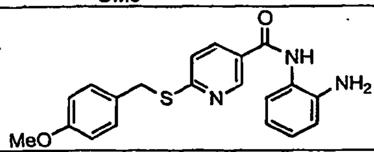
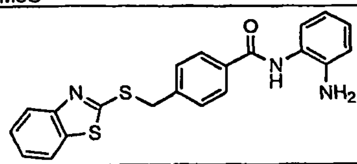
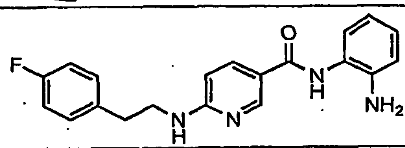
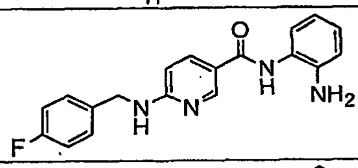
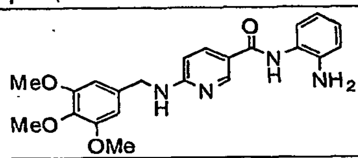
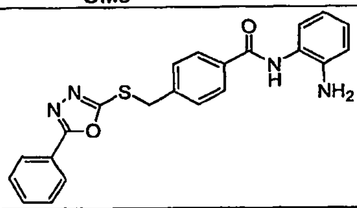
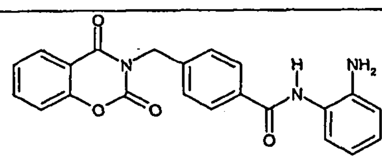
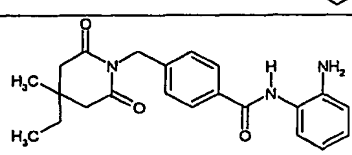
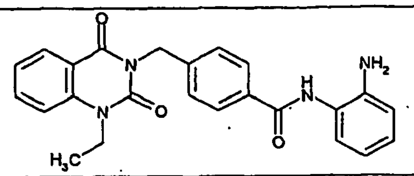
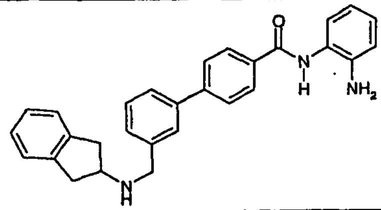
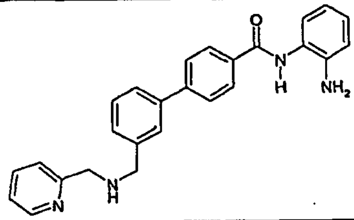
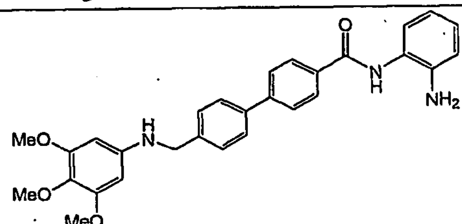
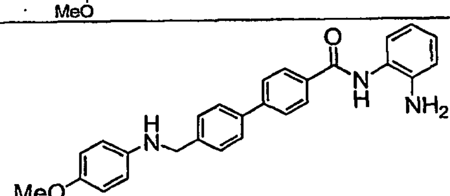
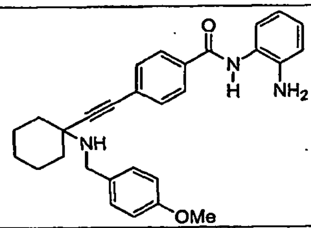
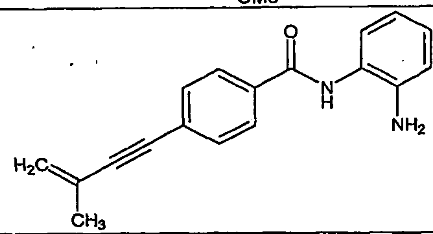
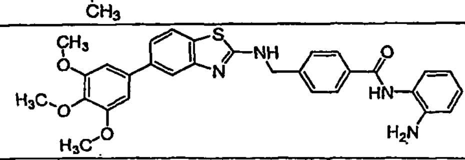
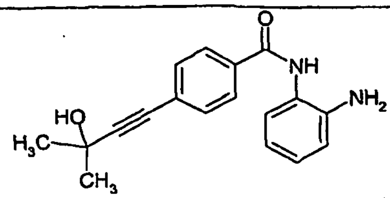
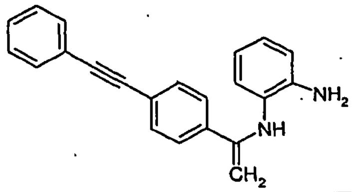
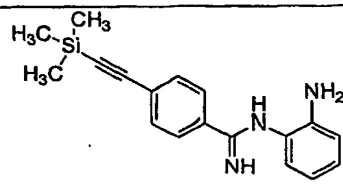
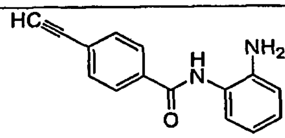
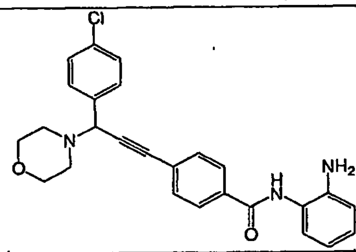
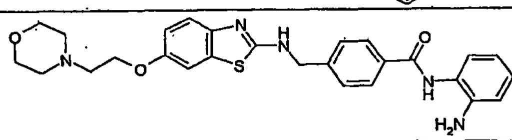
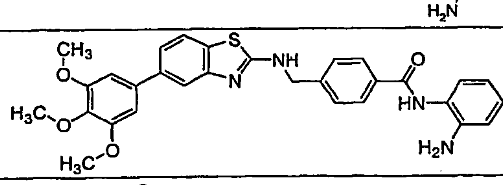
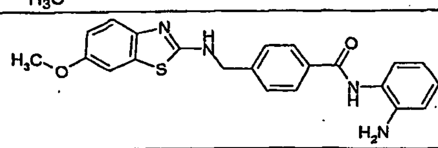
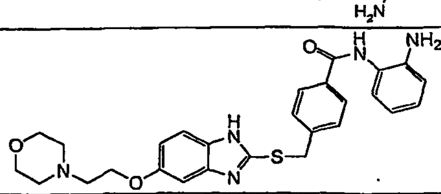
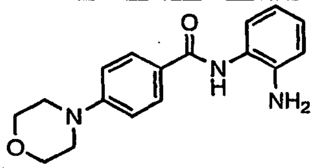
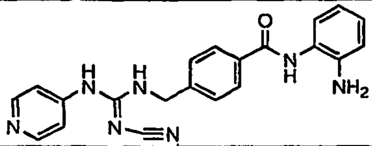
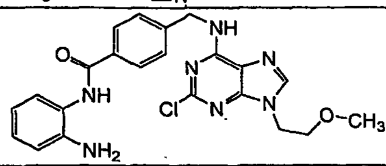
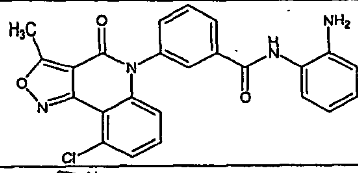
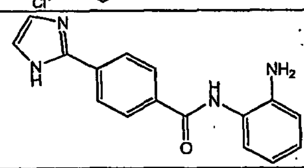
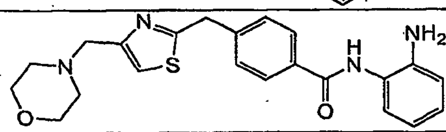
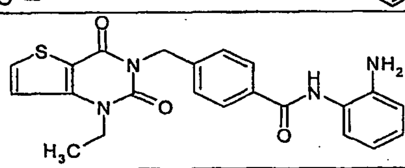
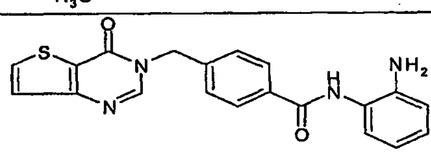
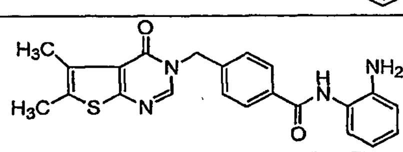
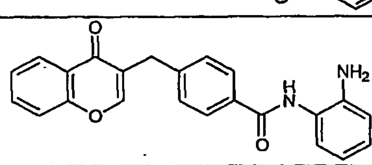
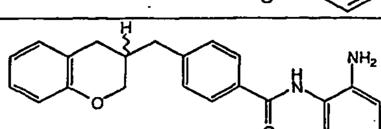
Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT(HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
169		0.3	0.7	1
171		8	3	25
172		0.4	1	3
174		4	0.4	5
175		4	0.5	3
176		5	1	3
177		1	0.4	1

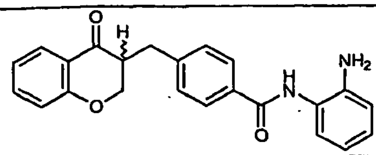
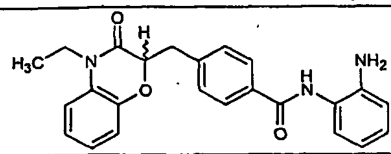
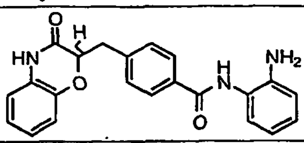
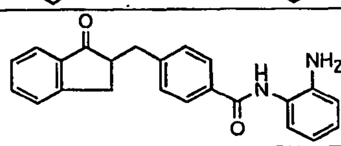
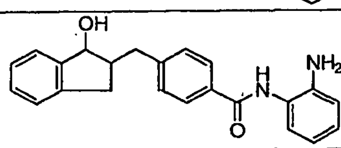
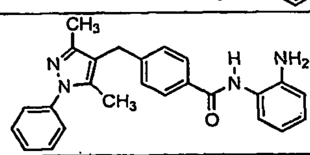
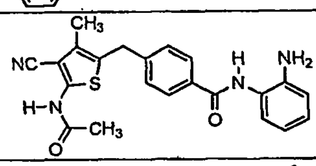
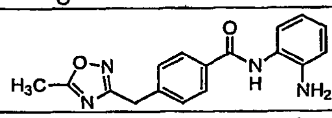
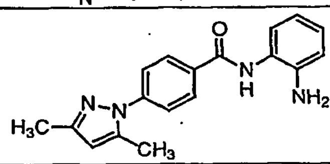
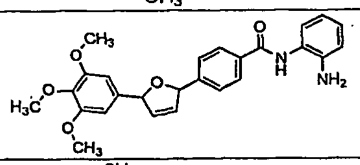
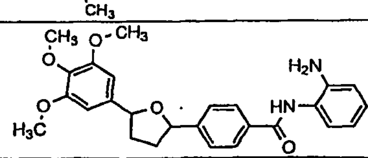
Table 5f

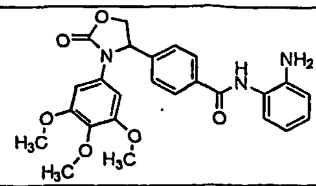
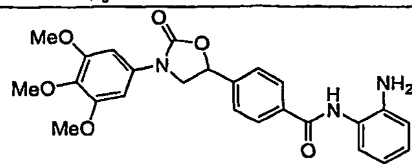
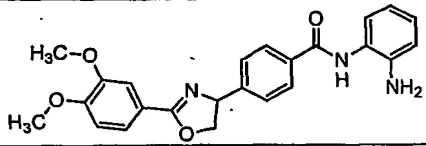
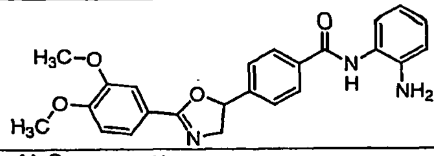
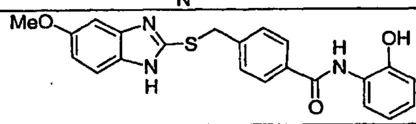
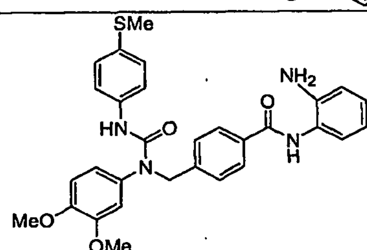
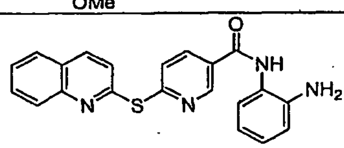
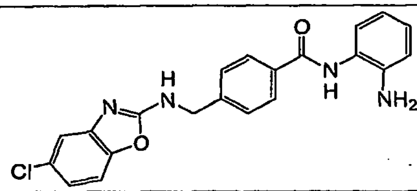
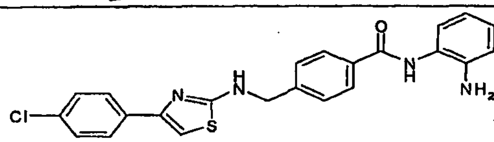
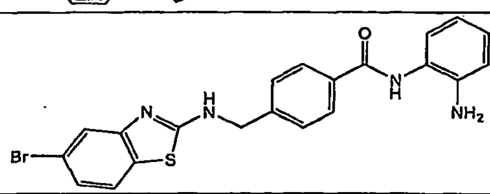
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
117	179		1	0.3	1
118	180		3	2	5

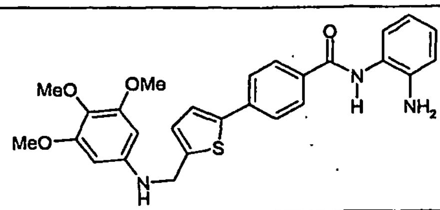
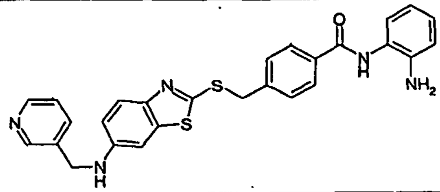
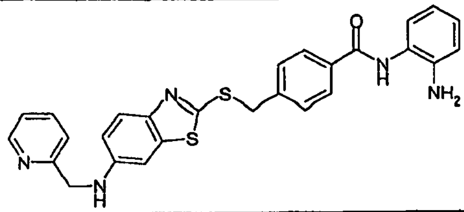
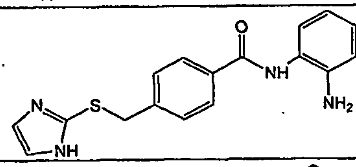
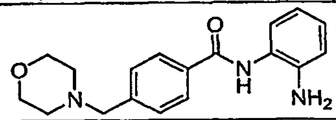
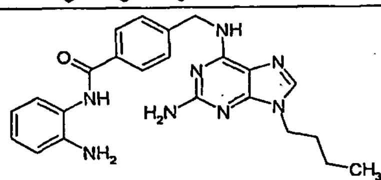
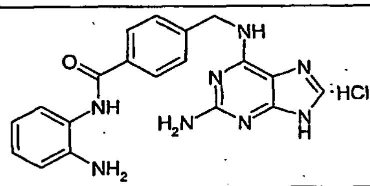
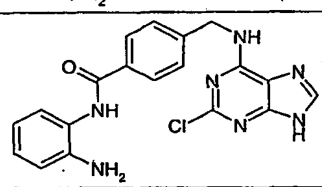
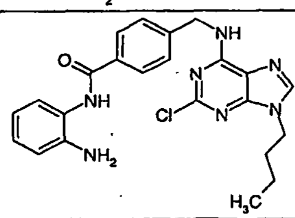
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
119	181		0.5	0.4	1
122	186		2	2	2
123	187		2	5	2
125	189		3	2	5
126	190		3	1	>5
127	192		2	1	3
128	193		4	16	
129	194		3	11	

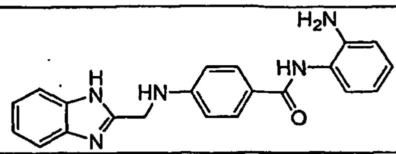
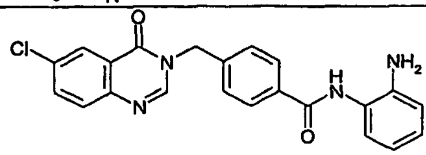
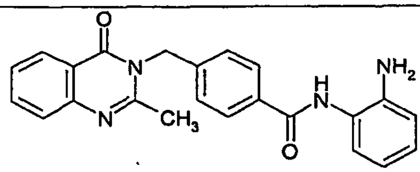
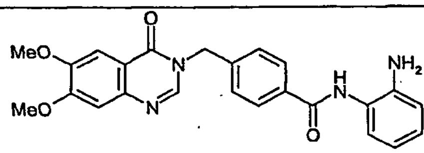
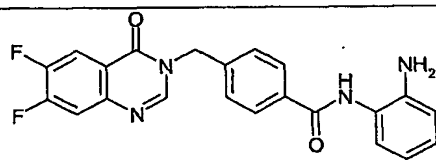
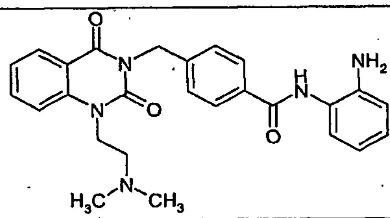
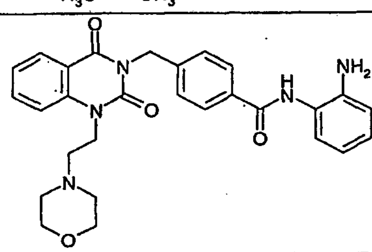
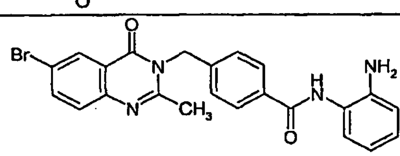
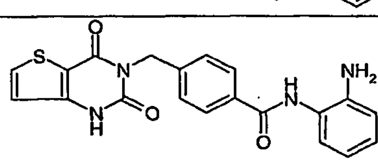
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
130	195		7	9	
131	196		4	3	
132	198		24	14	
133	199		7	9	
134	201		11	5	
144	228		3	0.3	1
145	231		4	1	3
146	233		0.9	0.3	1
147	236		5	6	

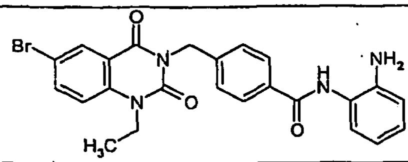
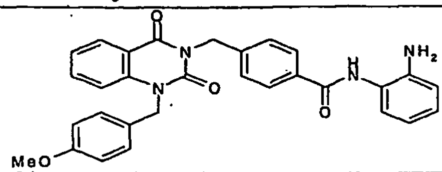
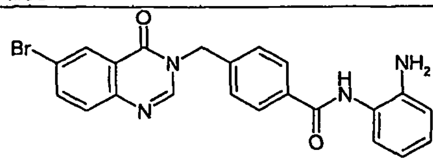
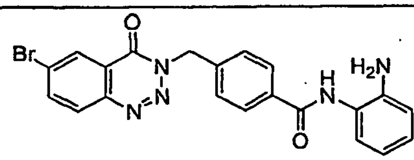
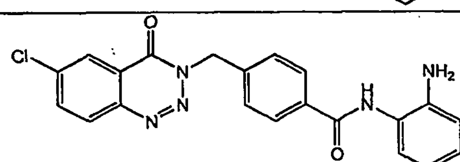
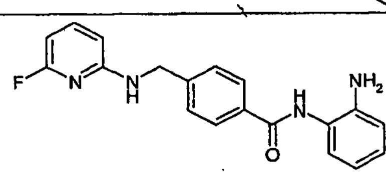
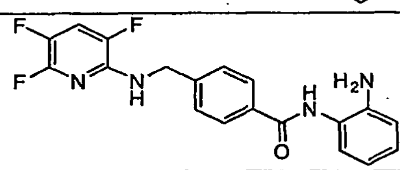
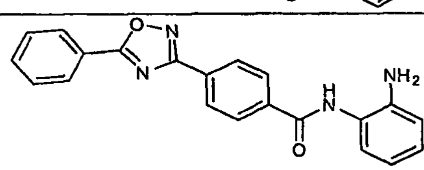
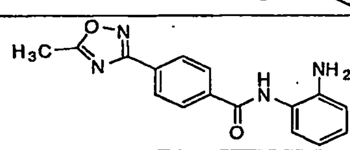
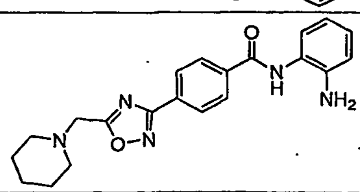
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
148	238		3	6	
149	240		1.8	10	
150	243		2	0.8	1
151	247		3	0.6	2
152	249		4	1	2
153	252		8	1	2
154	255		2	0.8	1
155	257		0.4	0.4	1
156	259		3	0.3	1
157	262		0.5	0.3	1
158	265		2	2	3

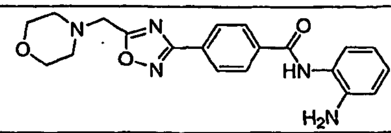
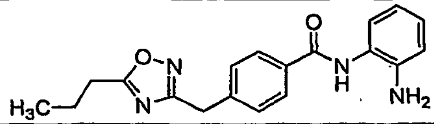
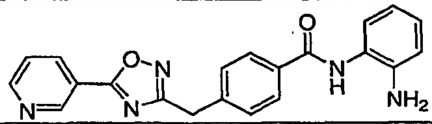
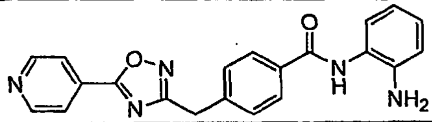
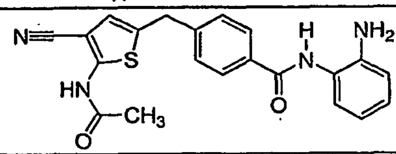
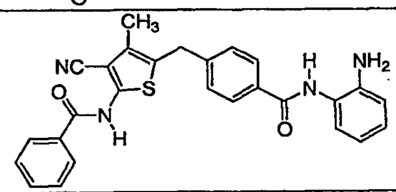
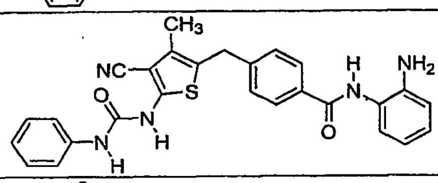
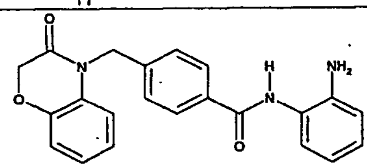
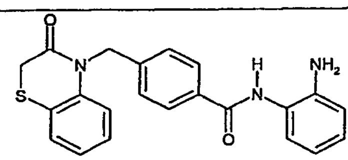
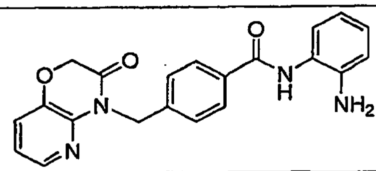
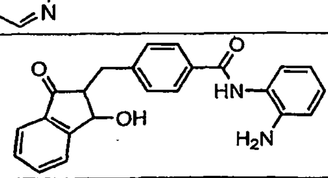
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
159	266		0.4	0.9	2
160	269		9	4	
161	270		4	1	5
162	272		2	0.6	<1
163	275		4	0.9	2
164	277		4	0.3	1
165	281		0.5	0.6	1
166	284		3	5	
167	286		5	2	
168	289		17	5	
169	290		11	3	

Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
170	296		20	7	
171	297		7	0.4	1
172	301		3	3	
173	305		4	2	
174	311		0.9	0.7	1
178	317		2	0.3	1
179	319		4	8	
180	320		2		1
181	321		0.5	0.3	5
182	322		0.7	0.4	2

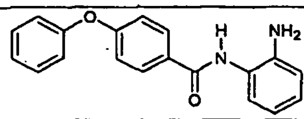
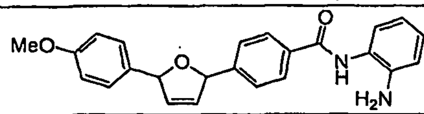
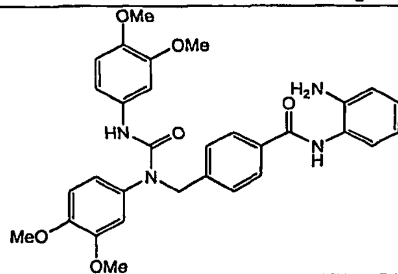
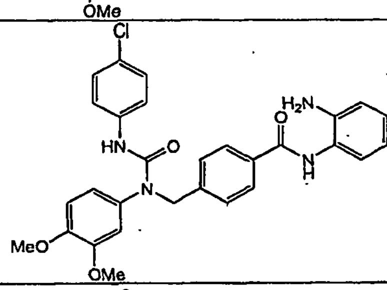
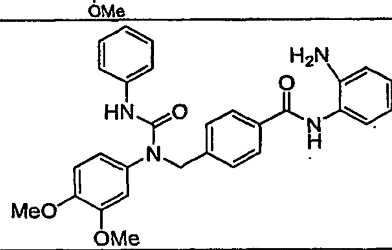
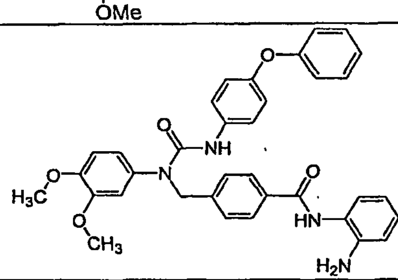
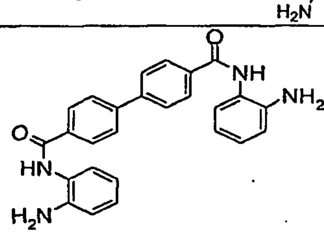
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
183	323		1	0.6	1
184	325		0.3	1	2
185	326		1	1	3
186	327		2	5	3
187	328		17	10	
189	330		3	2	1
190	331		4	10	
191	332		0.4	1	5
192	333		2	0.1	1

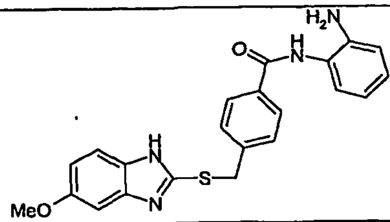
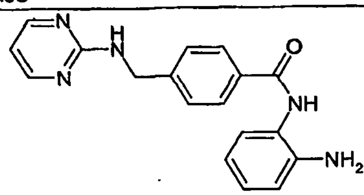
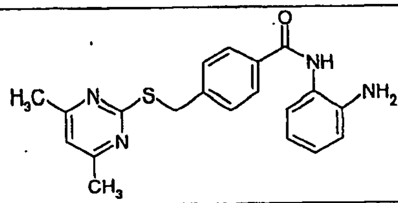
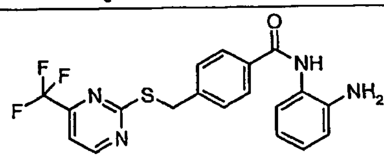
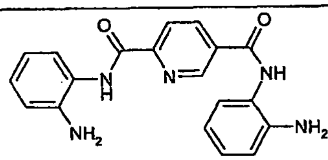
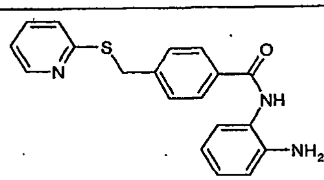
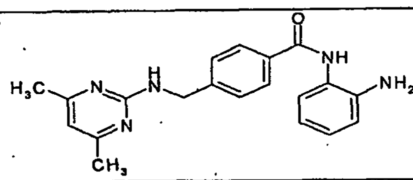
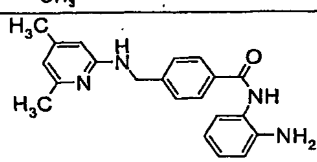
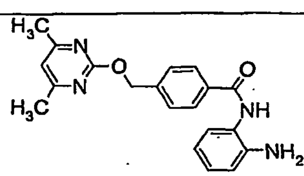
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
193	334		8	0.2	1
195	336		1	0.4	<1
196	337		3	0.6	1
197	338		2	0.5	3
198	339		4	3	
199	340		2	1	1
200	341		4	1	3
201	342		3	0.4	1
202	343		0.5	0.3	1

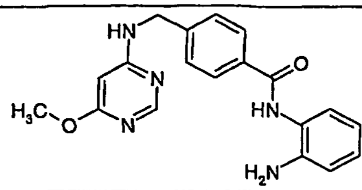
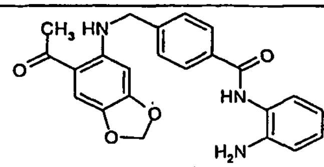
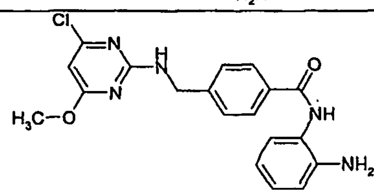
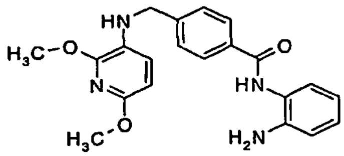
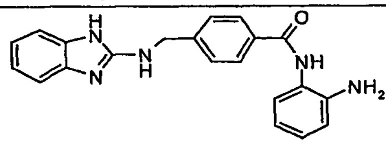
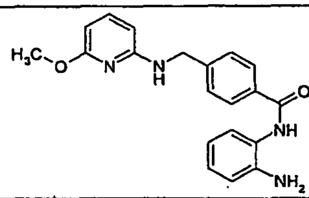
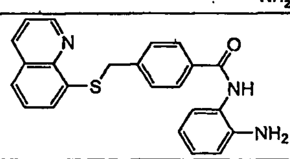
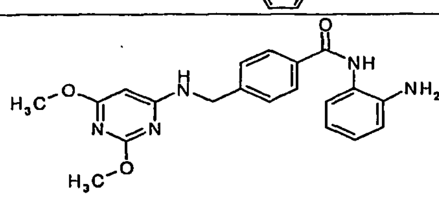
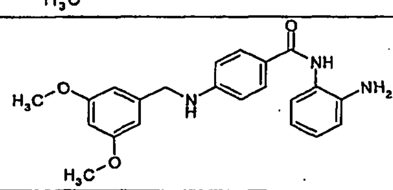
Ex	Cpd	Structure	Human HDAC-1 IC$_{50}$ (μM)	MTT (HCT116) IC$_{50}$ (μM)	H4 Ac (T24) EC$_{50}$ (μM)
203	344		0.5	0.2	1
204	345		0.4	0.8	1
205	346		3	0.5	<1
206	347		2	0.6	2
207	348		2	0.3	1
208	349		13	1	3
209	350		2	1	5
211	352		16	9	
212	353		3	10	
213	354		15	5	

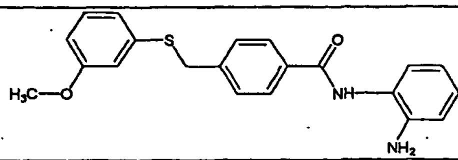
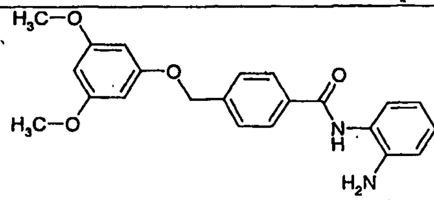
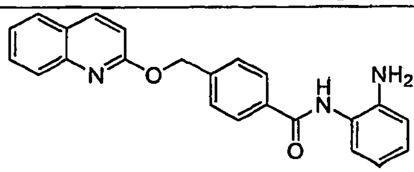
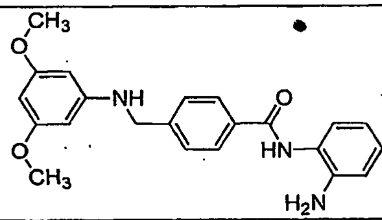
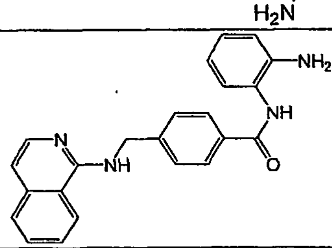
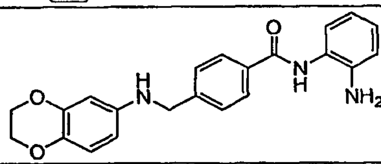
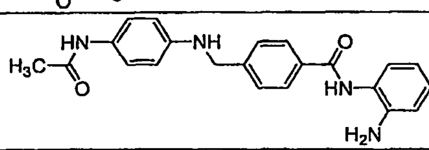
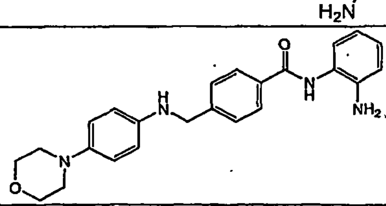
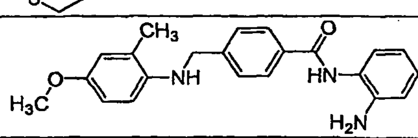
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
214	355		25	10	
215	356		5	2	
216	357		4	0.4	2
217	358		3	1	2
218	359		2	0.3	1
219	360		5	0.2	1
220	361		2	0.5	1
221	362		2	0.7	1
222	363		1	0.3	3
223	364		4	0.6	
224	365		3	0.6	3

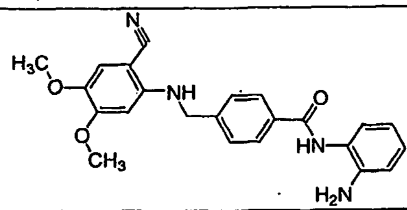
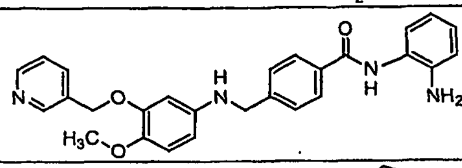
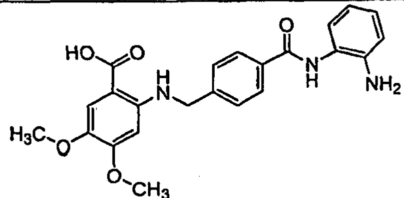
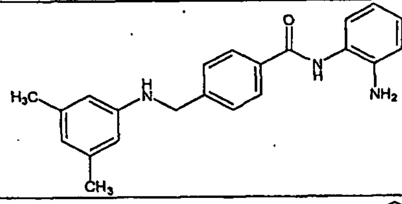
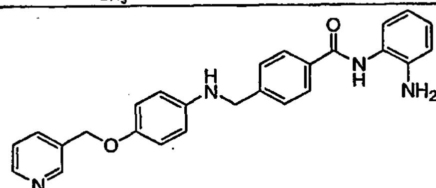
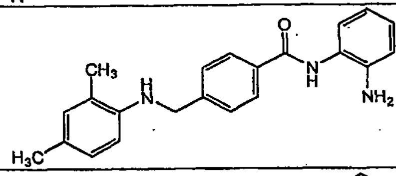
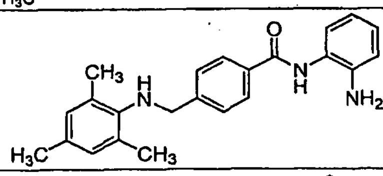
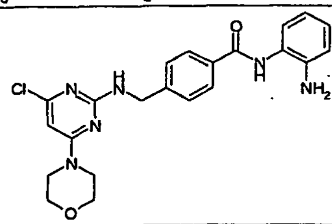
SUBSTITUTE SHEET (RULE 26)

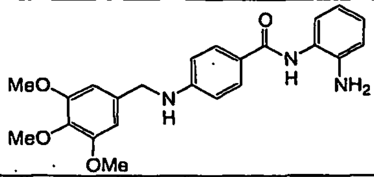
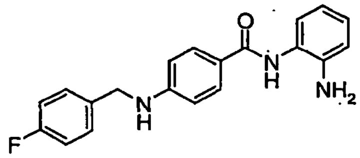
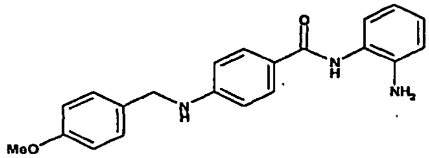
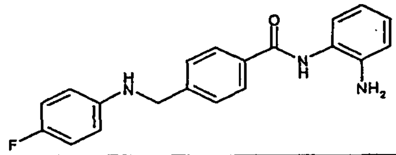
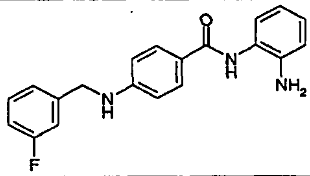
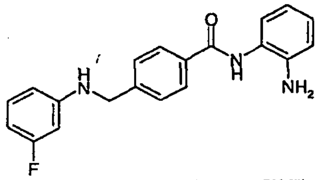
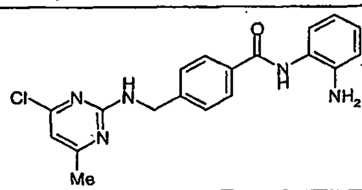
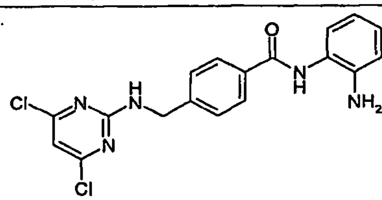
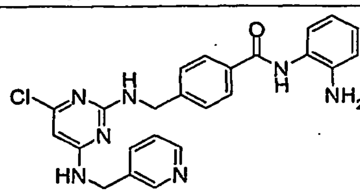
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
225	366		14	10	
226	367		6	2	5
230	371		4	0.5	2
231	372		2	0.2	1
232	373		4	0.4	1
233	374		2.5	0.3	1
234	375		3	4	25

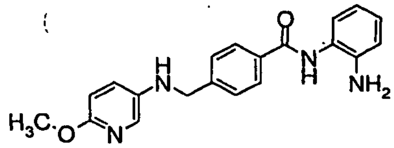
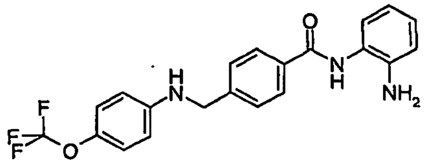
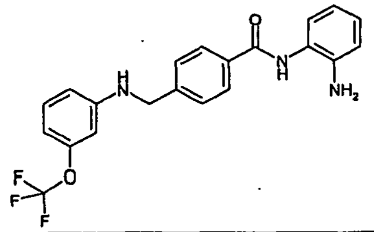
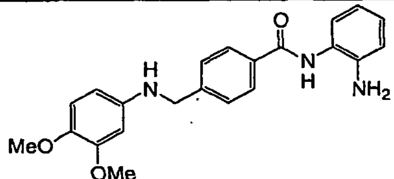
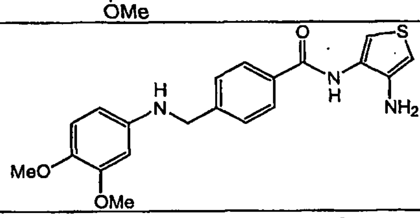
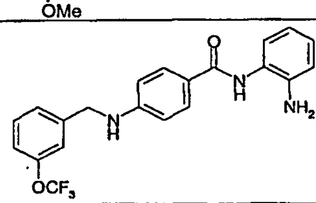
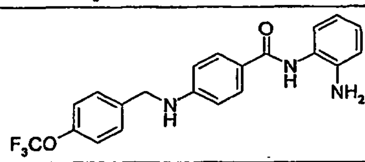
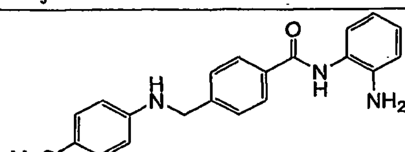
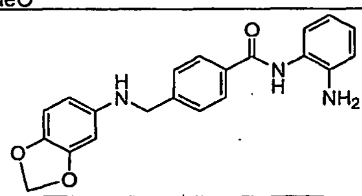
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
235	376		3	0.1	1
236	377		4	2	3
237	378		2	0.7	2
238	379		2	0.6	15
239	380		6	8	
240	381		2	1	2
241	382		3	1	3
242	383		2	0.5	2
243	384		3	2	5

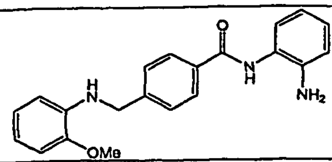
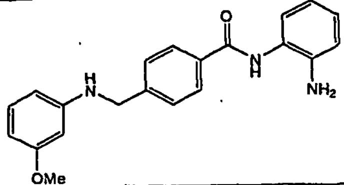
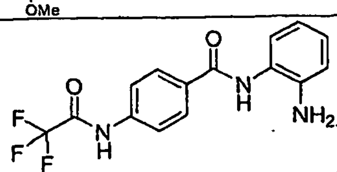
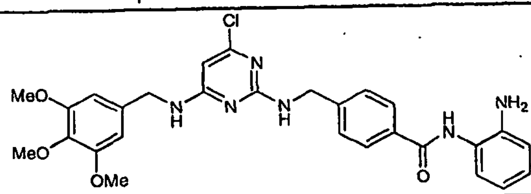
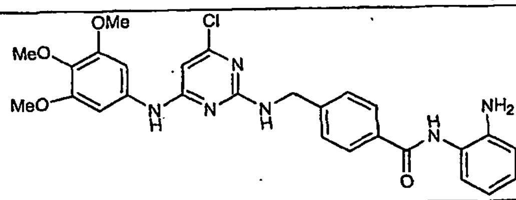
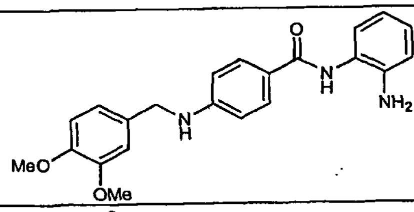
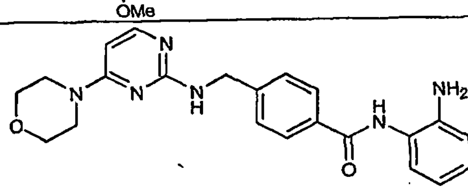
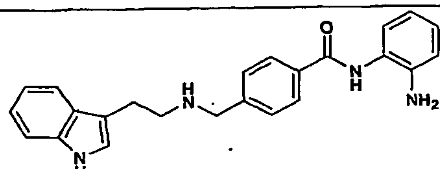
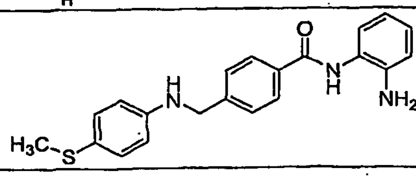
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
244	385		3	1	2
245	386		3	1	1
246	387		2	1	1
247	388		3	0.4	5
248	389		3	0.2	1
249	390		2	0.8	5
250	391		1	0.9	3
251	392		4	1	1
252	393		4	0.6	1

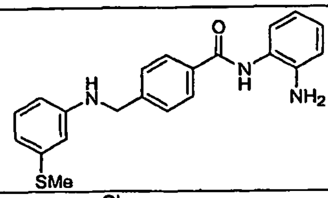
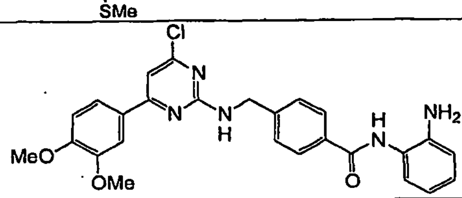
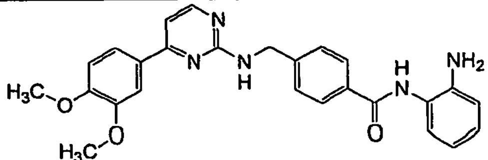
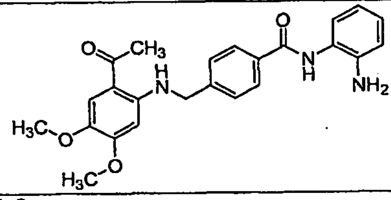
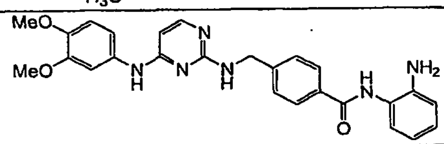
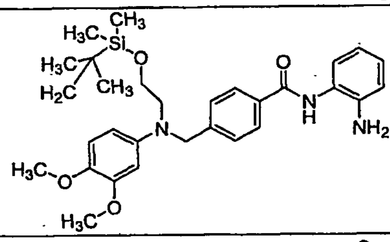
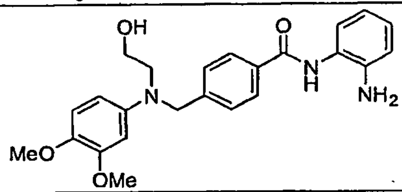
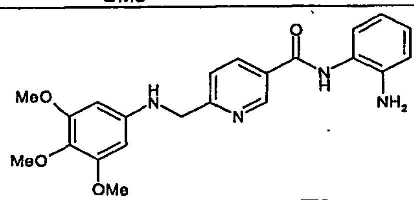
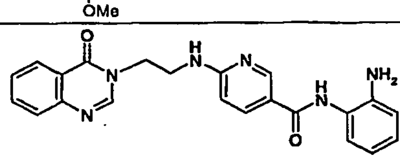
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
253	394		4	2	25
254	395		2	1	5
255	396		2	0.7	5
256	397		1	0.6	4
258	399		14	9	
259	400		8	0.3	2
260	401		6	0.3	2
261	402		14	0.4	1
262	403		1	0.2	1

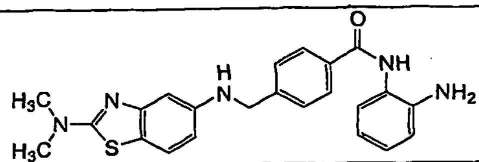
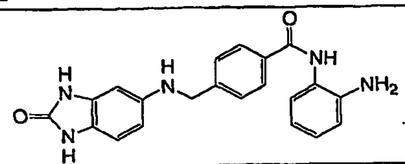
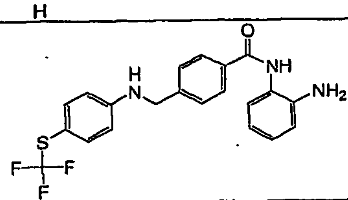
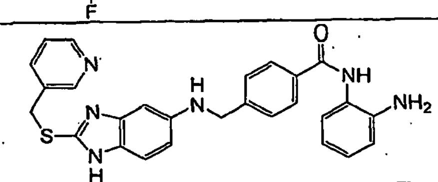
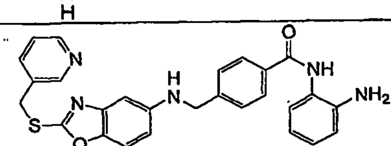
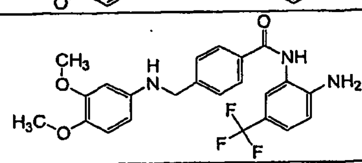
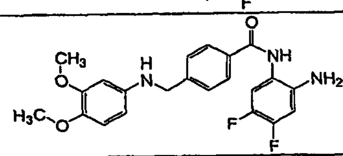
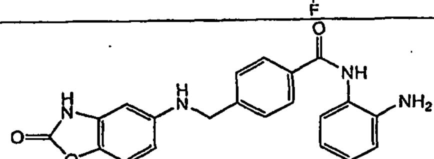
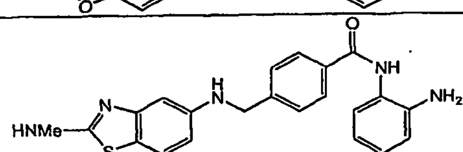
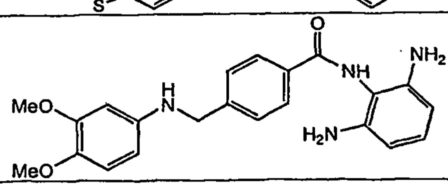
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
263	404		3	0.6	5
264	405		5	1	5
265	406		3	11	
266	407		3	2	
267	408		4	2	
268	409		3	1	9999
269	410		0.9	0.1	>5
270	411		2		1

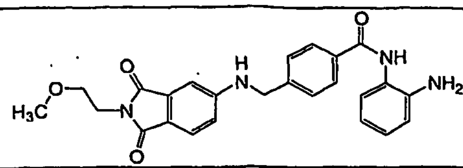
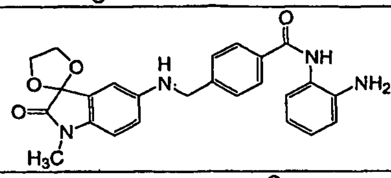
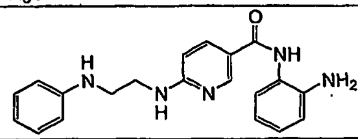
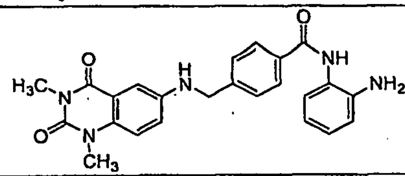
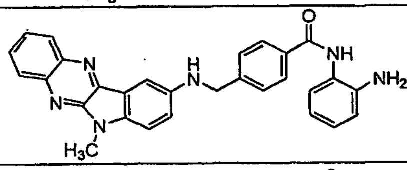
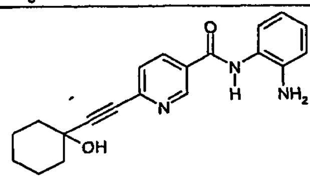
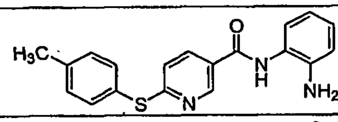
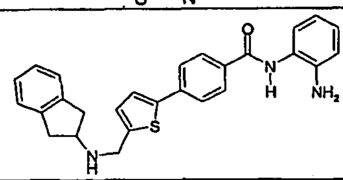
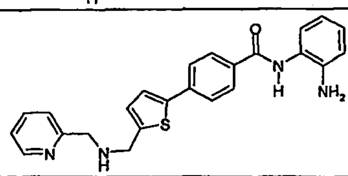
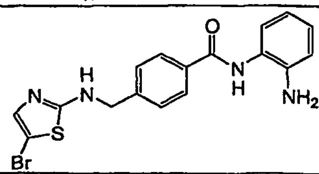
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
271	412		3	2	3
272	413		2	2	3
273	414		3	1	1
274	415		3	1	3
275	416		3	0.6	1
276	417		3	1	1
277	418		3	0.9	2
278	419		2	1	5
279	420		3	0.7	1

Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
280	421		4	0.6	1
281	422		<0.05	0.9	5
282	423		0.5	1	3
283a	424b		2	0.4	1
283b	424c		3	0.8	3
284	425		2	0.6	5
285	426		2	1	10
286	427		0.6	2	1
287	428		0.7	0.7	1

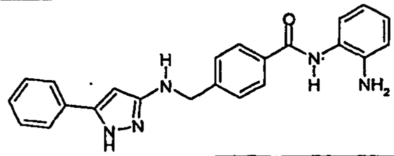
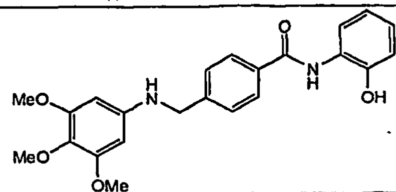
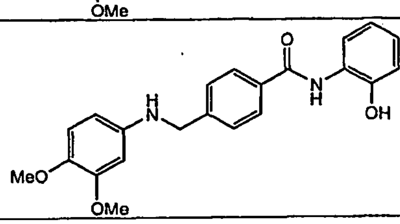
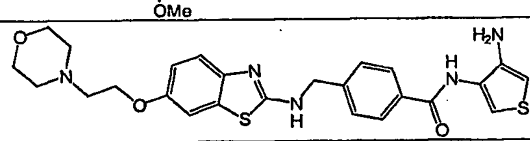
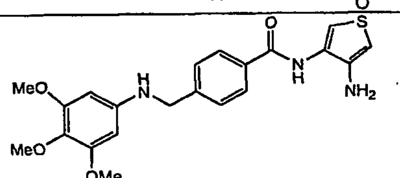
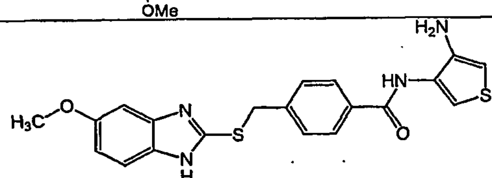
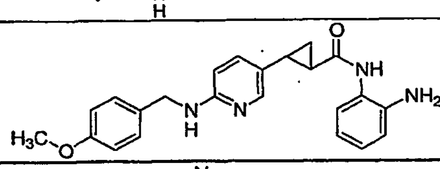
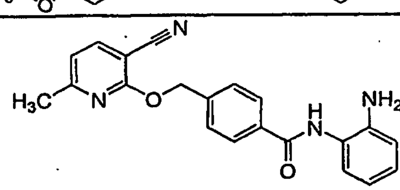
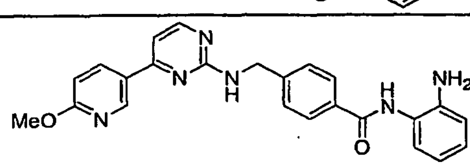
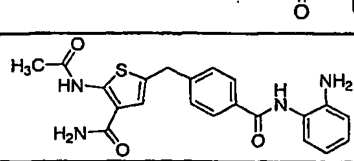
Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
288	429		4	0.9	1
289	430		5	0.7	1
290	431		5	5	
291	432		2	1	3
292	432		2	0.6	1
293	434		4	0.6	2
294	435		3	0.6	1
295	436		5	0.8	5
296	437		3	0.4	1

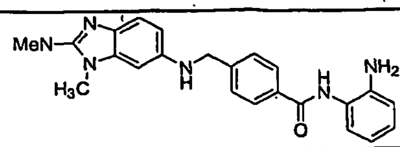
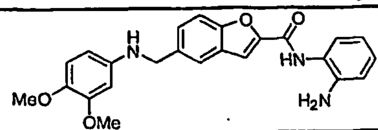
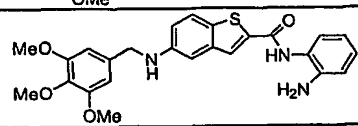
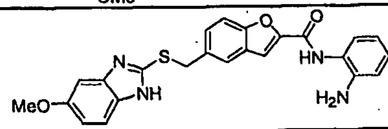
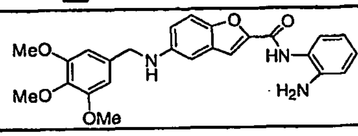
Ex	Cpd	Structure	Human HDAC-1 IC$_{50}$ (μM)	MTT (HCT116) IC$_{50}$ (μM)	H4 Ac (T24) EC$_{50}$ (μM)
297	438		5	0.6	1
298	439		3	0.4	1
299	440		4	0.1	2
300	441		2	0.8	2
301	442		17	0.4	1
302	443				
303	444				
304	445		16	6	
305	446		21	7	

Ex	Cpd	Structure	Human HDAC-1 IC50 (μM)	MTT (HCT116) IC50 (μM)	H4 Ac (T24) EC50 (μM)
307	448		3	0.2	2
308	449		1	6	
309	450		3	2	
310	451		4	0.2	3
311	452		3	0.3	2
312	453		9999	37	
313	454		4	2	5
314	455		4	0.7	1
315	456		3	0.4	8888
316	457		9999	9999	

Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
317	458		3	0.3	2
318	459		4	0.3	1
319	460		3	1	1
320	461		1.4	0.3	1
321	462		4	0.3	1
322	463		12	6	
323	464		4	11	
324	465		2	9999	9999
325	466		3	2	1
326	467		4	0.4	2

SUBSTITUTE SHEET (RULE 26)

Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
327	468		2	8	<1
426	571		4	11	
427	572		1.5	5	5
428	573		7	0.4	1
429	574		13	0.7	3
430	575		2	0.2	1
431	576		5	6	
432	577		2	0.5	2
433	578		0.6	0.1	1
434	579		2	0.5	1

Ex	Cpd	Structure	Human HDAC-1 IC_{50} (μM)	MTT (HCT116) IC_{50} (μM)	H4 Ac (T24) EC_{50} (μM)
435	580		4	0.3	<1
436	587		5	0.8	2
437	590		2	2	3
438	591		4	0.3	<1
439	592		5	0.4	<1

Assay Example 2

Antineoplastic Effects of Histone Deacetylase Inhibitors on Human Tumor Xenografts *In Vivo*

[0413] Eight to ten week old female BALB/c nude mice (Taconic Labs, Great Barrington, NY) were injected subcutaneously in the flank area with 2 x 10^6 preconditioned HCT116 human colorectal carcinoma cells. Preconditioning of these cells was done by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 30 mgs were excised and implanted subcutaneously in mice, in the left flank area, under Forene anesthesia (Abbott Labs, Geneve, Switzerland). When the tumors reached a mean volume of 100 mm^3, the mice were treated intravenously, subcutaneously, or intraperitoneally by daily injection, with a solution of the histone deacetylase inhibitor in an appropriate vehicle, such as PBS, DMSO/water, or Tween 80/water, at a starting dose of 10 mg/kg. The optimal dose of the HDAC inhibitor was established by dose response experiments according to standard protocols. Tumor volume was calculated every second day post infusion according to standard methods (*e.g.*, Meyer *et al.*, *Int. J. Cancer* **43**: 851-856 (1989)). Treatment with the HDAC inhibitors according to the invention caused a significant reduction in tumor weight and volume

relative to controls treated with vehicle only (*i.e.*, no HDAC inhibitor). In addition, the level of histone acetylation when measured was significantly elevated relative to controls. Data for selected compounds are presented in Table 6. FIG. 1 shows the full experimental results for compound **106**, which inhibits tumor growth by 80%. Figs. 2-10 show the results of additional compounds tested.

Table 6

Antitumor Activity in HCT 116 Colorectal Tumor Model *In Vivo*

Compound	% Inhibition of Tumor Growth
106	80[a]
126	62[b]
9	51[b]
87	30[b]
157	66[a]
167	58[a]
15	26[b]
168	26[b]
16	50[b]
154	23[a]
98	52[a]

a: 20 mg/kg i.p.
b: 40 mg/kg i.p.

Table 7

Antineoplastic Effects Of Histone Deacetylase Inhibitors On Nude Mice Xenograft Models

	% Inhibition Of Tumor Growth				
cpd	A 549 (p.o.)	SW48 (p.o.)	A 549 (i.p.)	HCT 116 (i.p.)	SW 48 (i.p.)
106	40% (70 mg/kg)	16% (60 mg/kg)	-	-	-
164	42% (70 mg/kg)	62% (60 mg/kg)	-	37% (20 mg/kg)	99% (25 mg/kg)
228	45% (70 mg/kg)	25% (60 mg/kg)	64% (20 mg/kg)	45% (20 mg/kg)	68% (20 mg/kg)
424 b	67% (50 mg/kg)	78% (30 mg/kg)	60% (50 mg/kg)	77% (75 mg/kg)	68% (25 mg/kg)

Assay Example 3

Combined Antineoplastic Effect of Histone Deacetylase Inhibitors and Histone Deacetylase Antisense Oligonucleotides on Tumor Cells *In Vivo*

[0414] The purpose of this example is to illustrate the ability of the combined use of a histone deacetylase inhibitor of the invention and a histone deacetylase antisense oligonucleotide to enhance inhibition of tumor growth in a mammal. Preferably, the antisense oligonucleotide and the HDAC inhibitor inhibit the expression and activity of the same histone deacetylase.

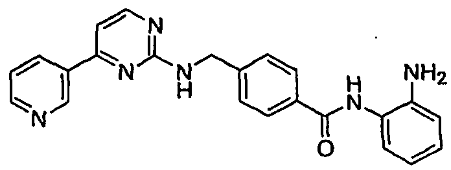
[0415] As described in Example 126, mice bearing implanted HCT116 tumors (mean volume 100 mm^3) are treated daily with saline preparations containing from about 0.1 mg to about 30 mg per kg body weight of histone deacetylase antisense oligonucleotide. A second group of mice is treated daily with pharmaceutically acceptable preparations containing from about 0.01 mg to about 5 mg per kg body weight of HDAC inhibitor.

[0416] Some mice receive both the antisense oligonucleotide and the HDAC inhibitor. Of these mice, one group may receive the antisense oligonucleotide and the HDAC inhibitor simultaneously intravenously via the tail vein. Another group may receive the antisense oligonucleotide via the tail vein, and the HDAC inhibitor subcutaneously. Yet another group may receive both the antisense oligonucleotide and the HDAC inhibitor subcutaneously. Control groups of mice are similarly established which receive no treatment (*e.g.*, saline only), a mismatch antisense oligonucleotide only, a control compound that does not inhibit histone deacetylase activity, and a mismatch antisense oligonucleotide with a control compound.

[0417] Tumor volume is measured with calipers. Treatment with the antisense oligonucleotide plus the histone deacetylase protein inhibitor according to the invention causes a significant reduction in tumor weight and volume relative to controls.

We claim:

1. A histone deacetylase inhibitor of formula (1):

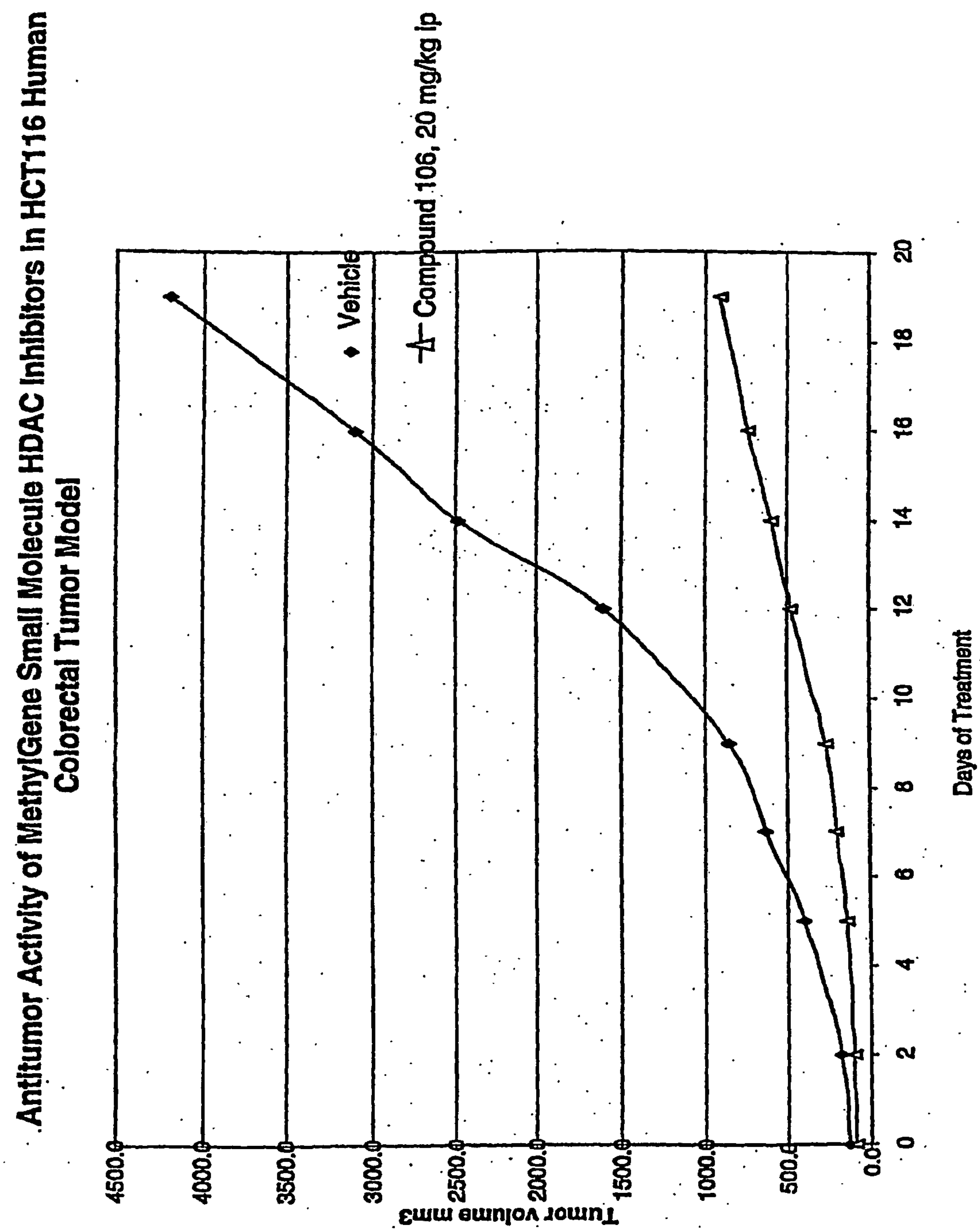


or pharmaceutically acceptable salt.

2. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

3. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a compound according to claim 1.

4. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a composition according to claim 2.



Antitumor Activity of MethylGene Small Molecule HDAC Inhibitors in HCT116 Human Colorectal Tumor Model
Vehicle
Compound 106, 20 mg/kg ip
Tumor volume mm3
4500.0
4000.0
3500.0
3000.0
2500.0
2000.0
1500.0
1000.0
500.0
0.0
0
2
4
6
8
10
12
14
16
18
20
Days of Treatment

FIG. 1

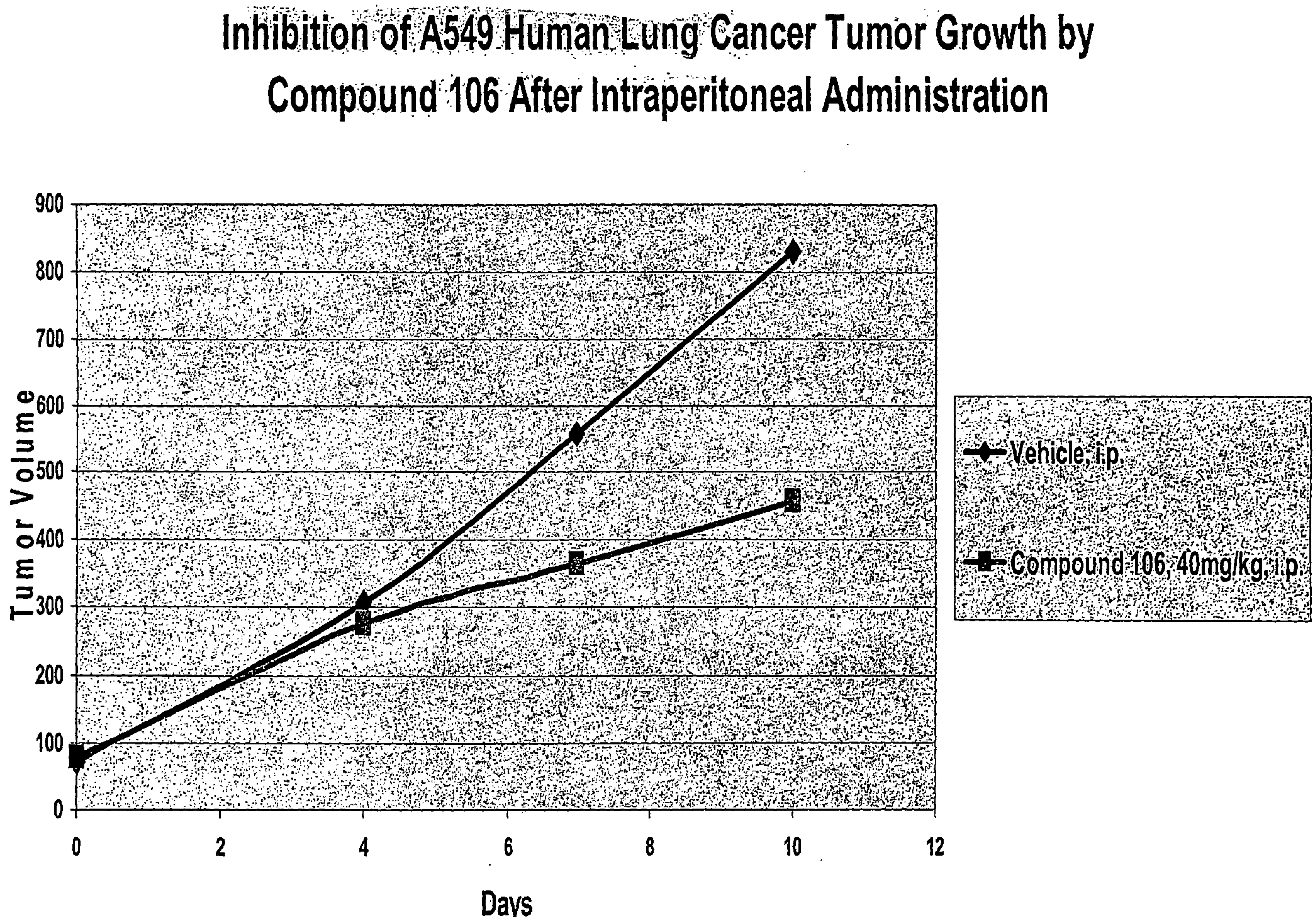

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 106 After Intraperitoneal Administration
Tumor Volume
900
800
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
Days
Vehicle, i.p.
Compound 106, 40mg/kg, i.p.

Fig. 2

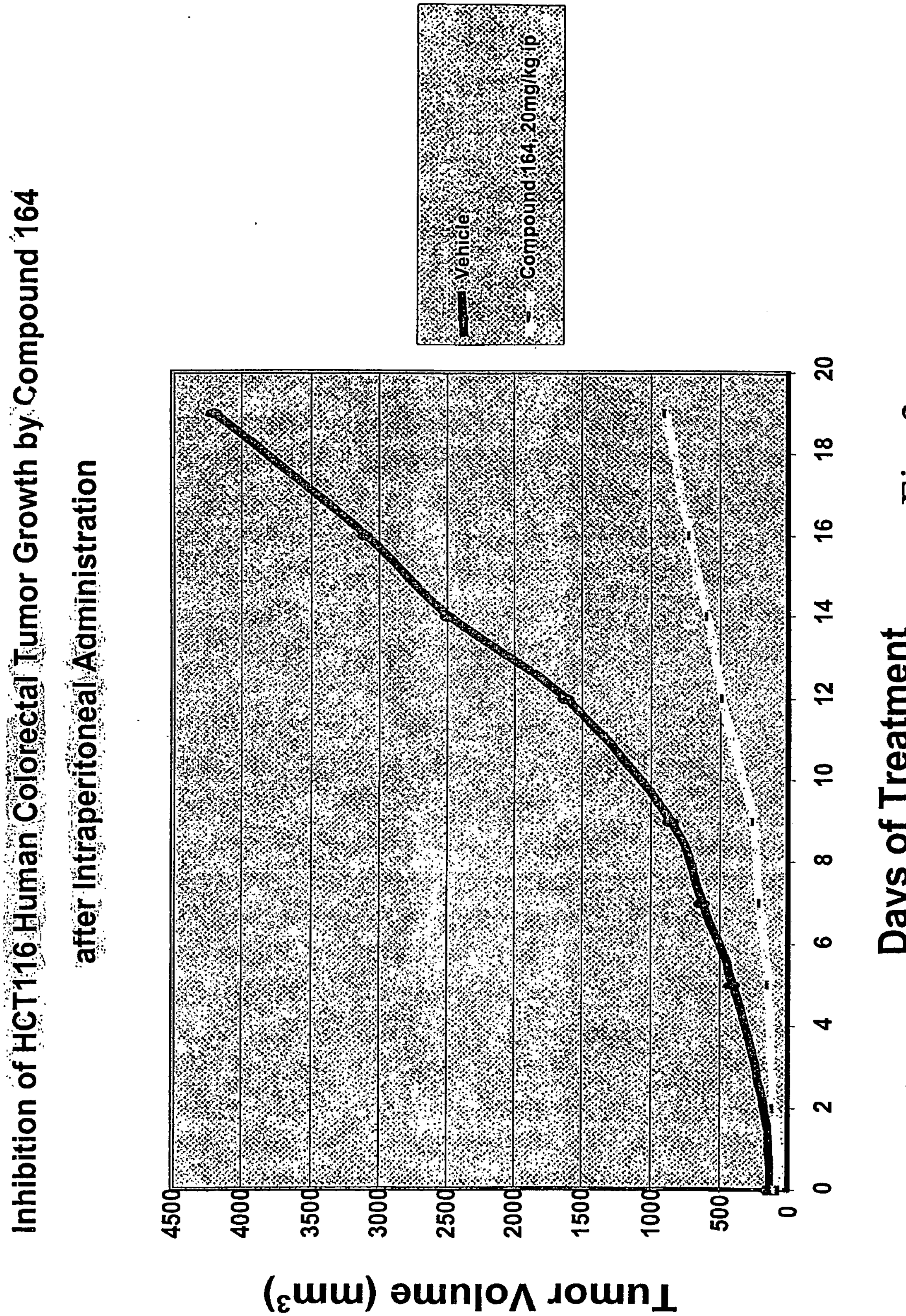

Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 164
after Intraperitoneal Administration
Vehicle
Compound 164, 20mg/kg ip
Tumor Volume (mm3)
0
500
1000
1500
2000
2500
3000
3500
4000
4500
0
2
4
6
8
10
12
14
16
18
20
Days of Treatment

Fig. 3

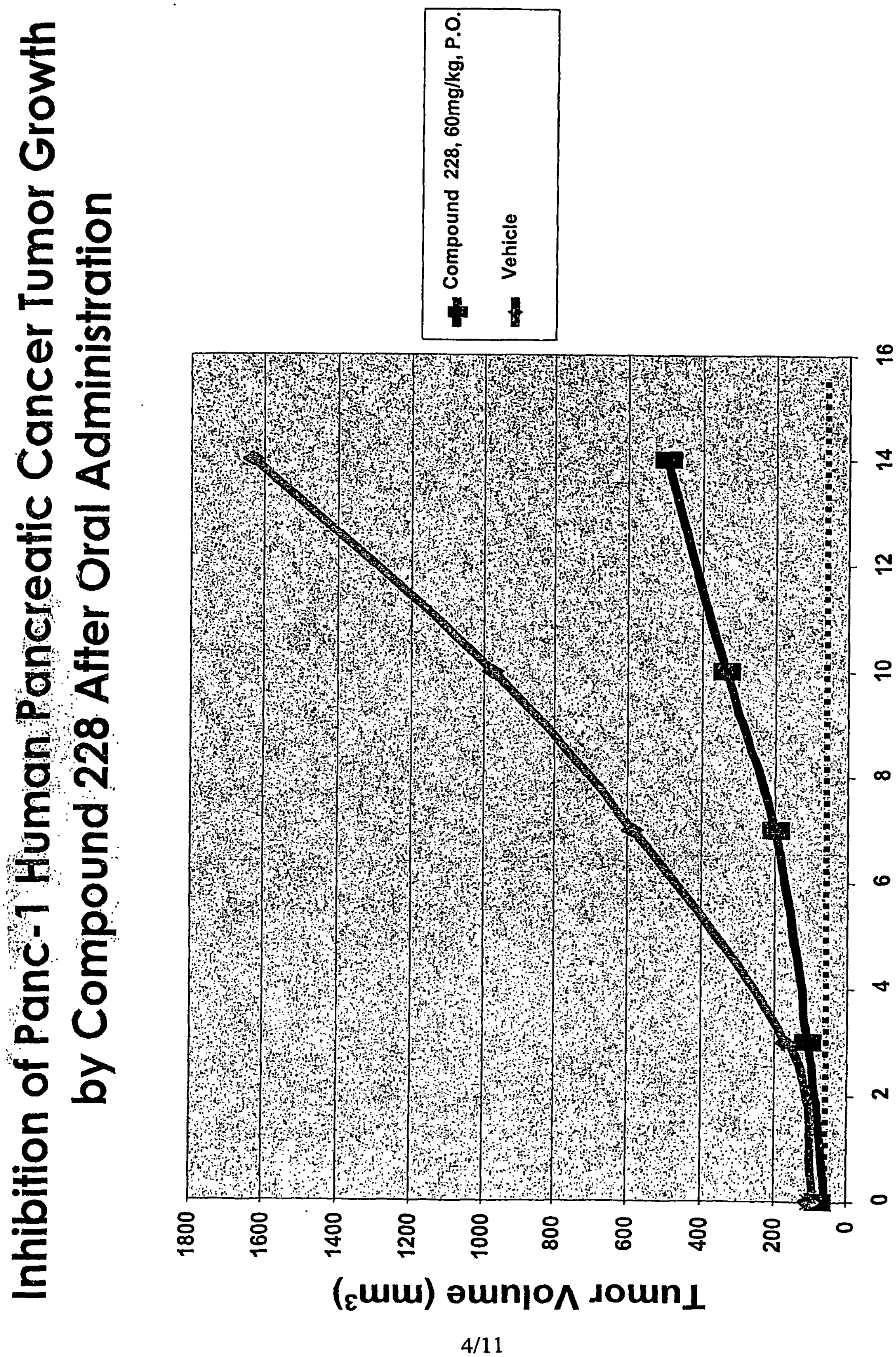

Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth
by Compound 228 After Oral Administration
Tumor Volume (mm3)
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
16
Days
Compound 228, 60mg/kg, P.O.
Vehicle

Fig. 4

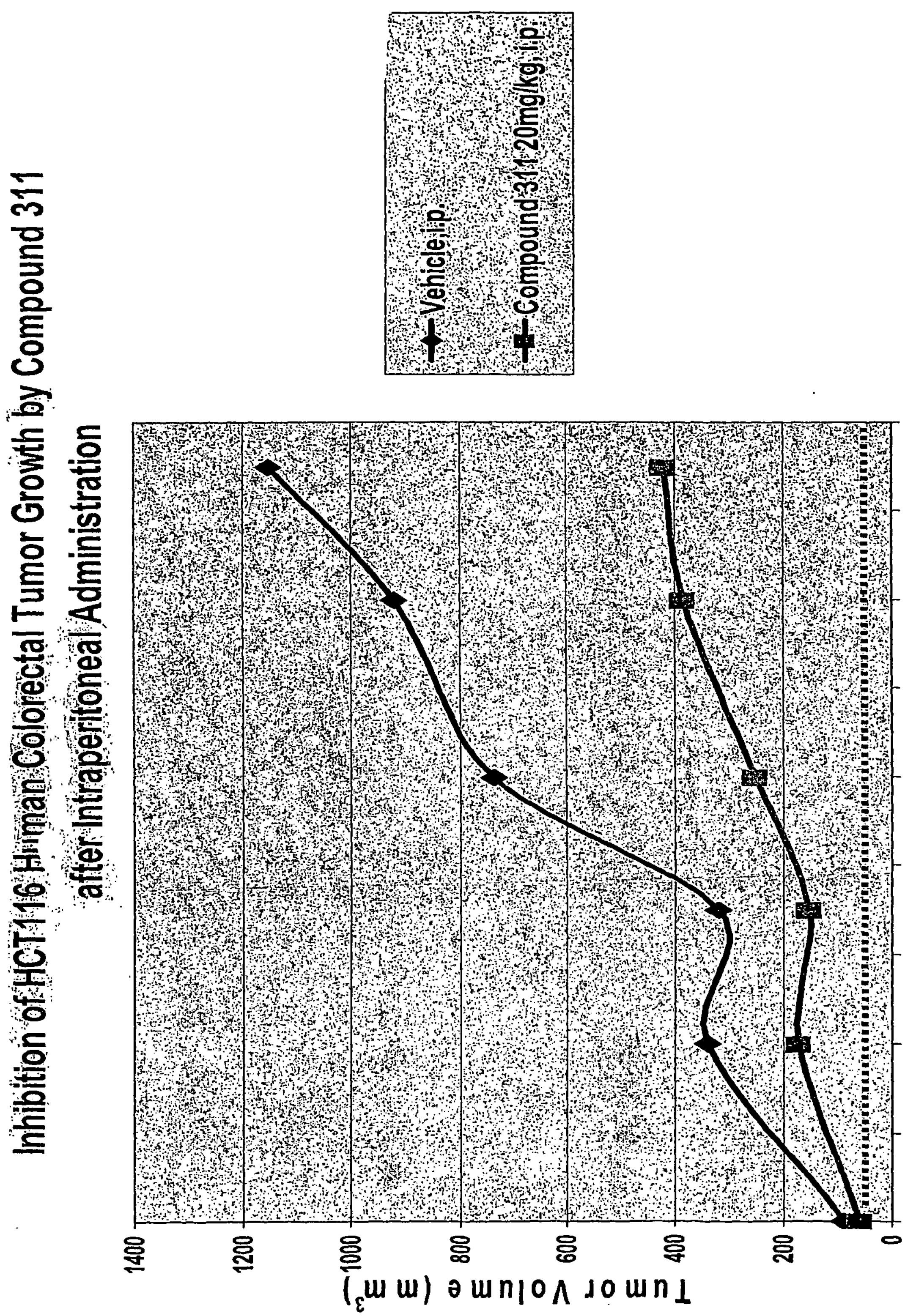

Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 311
after Intraperitoneal Administration
Vehicle,i.p.
Compound 311 20mg/kg, i.p.
Tumor Volume (m m³)
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
16
18
Days

Fig. 5

Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 376 After Oral Administration

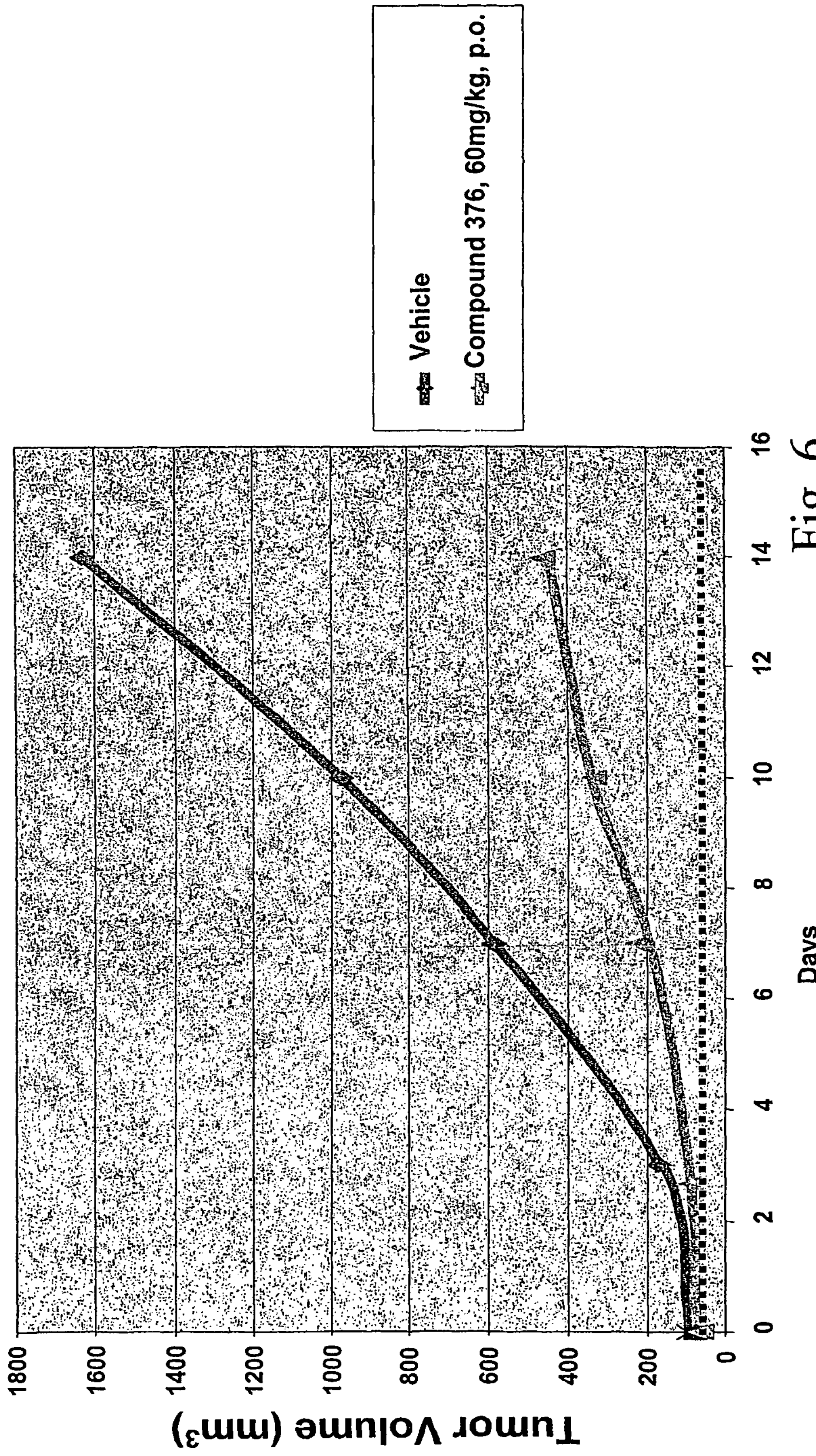


Fig. 6

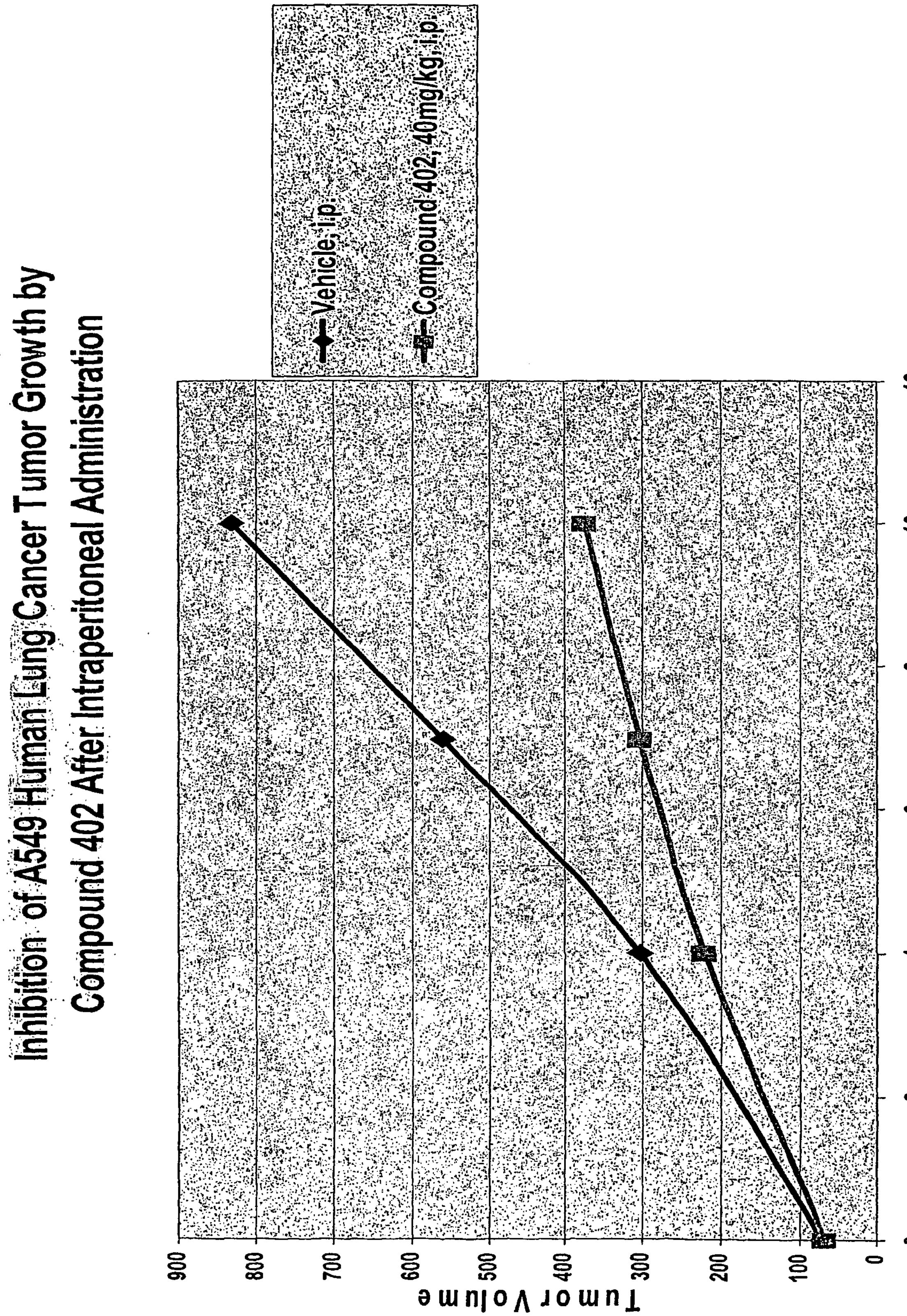
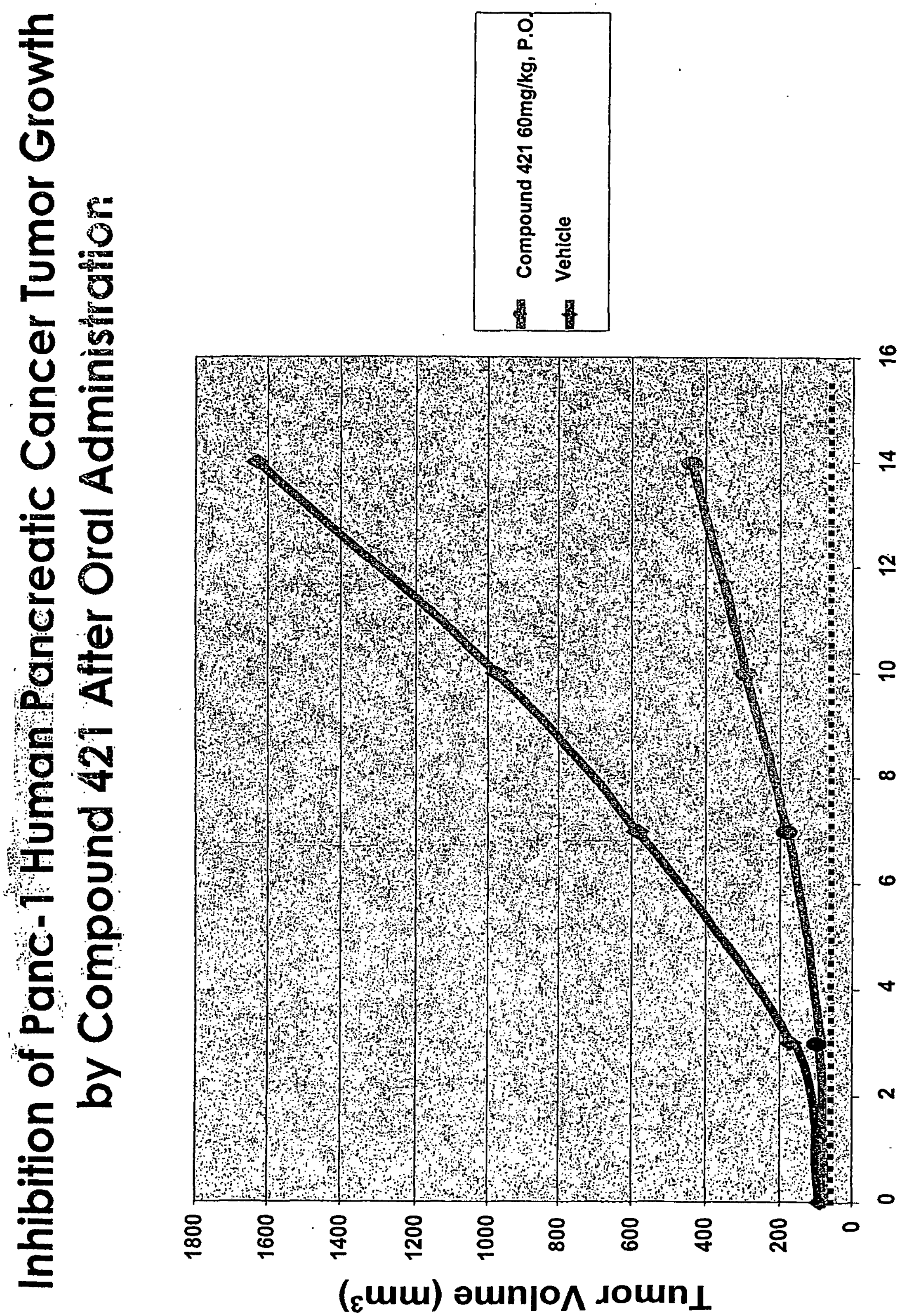

Inhibition of A549 Human Lung Cancer Tumor Growth by
Compound 402 After Intraperitoneal Administration
Vehicle, i.p
Compound 402, 40mg/kg, i.p.
Tumor Volume
Days
900
800
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12

Fig. 7



Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 421 After Oral Administration
Tumor Volume (mm³)
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
16
Days
Compound 421 60mg/kg, P.O.
Vehicle

Fig. 8

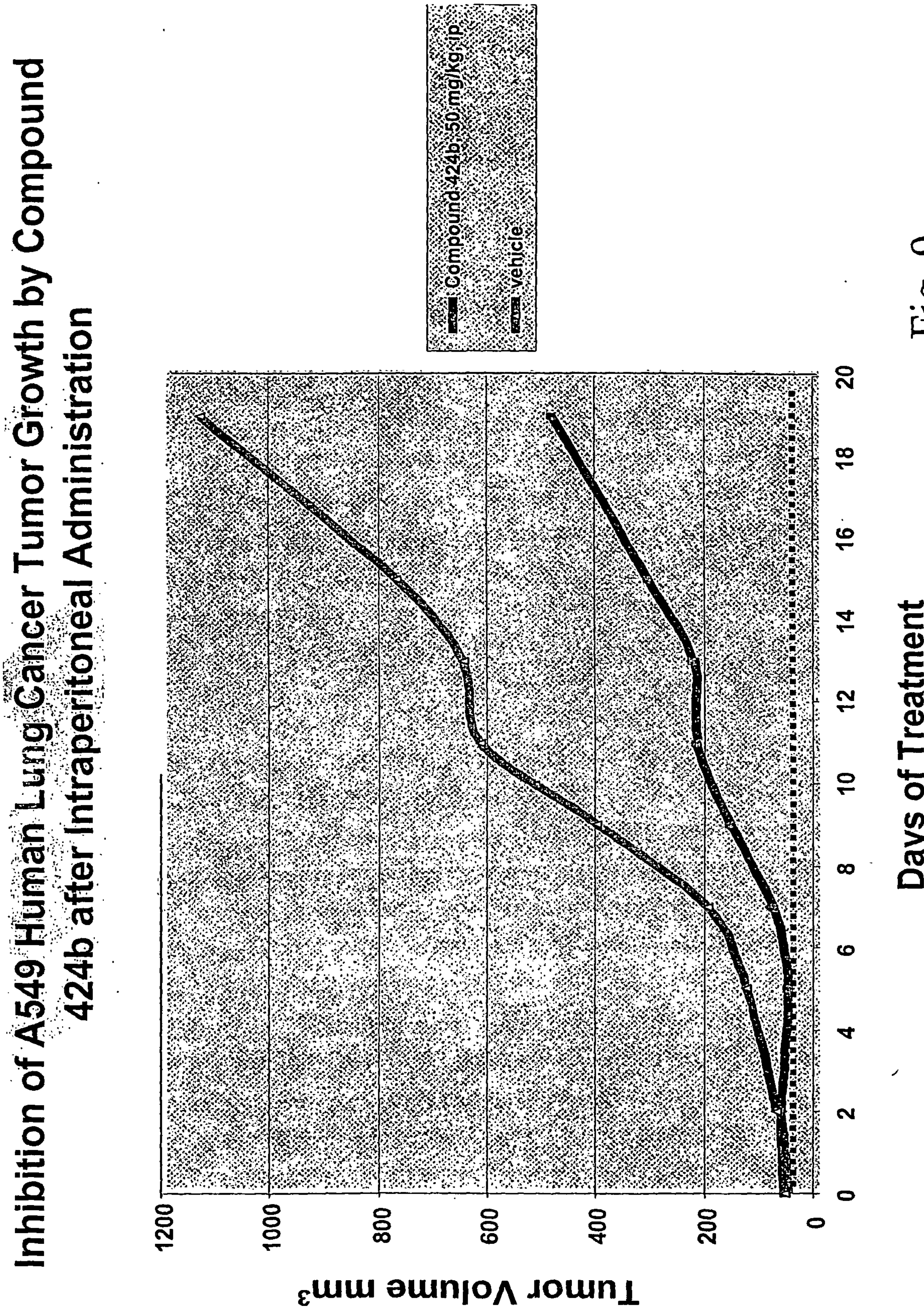
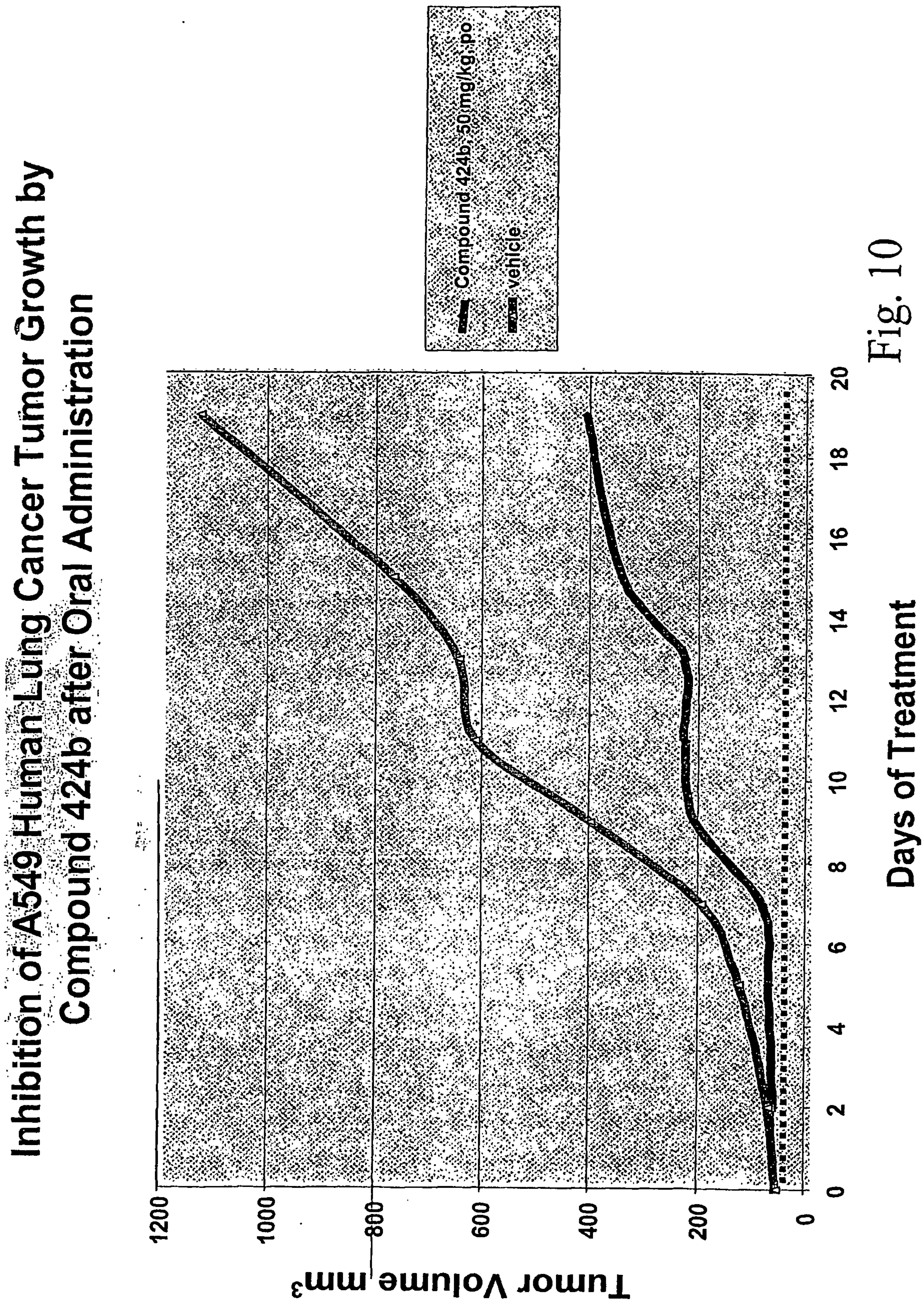

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Intraperitoneal Administration
Tumor Volume mm3
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
16
18
20
Days of Treatment
Compound 424b, 50 mg/kg, ip
Vehicle

Fig. 9



Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Oral Administration
Tumor Volume mm^3
0
200
400
600
800
1000
1200
0
2
4
6
8
10
12
14
16
18
20
Days of Treatment
Compound 424b, 50mg/kg, po
vehicle

Fig. 10

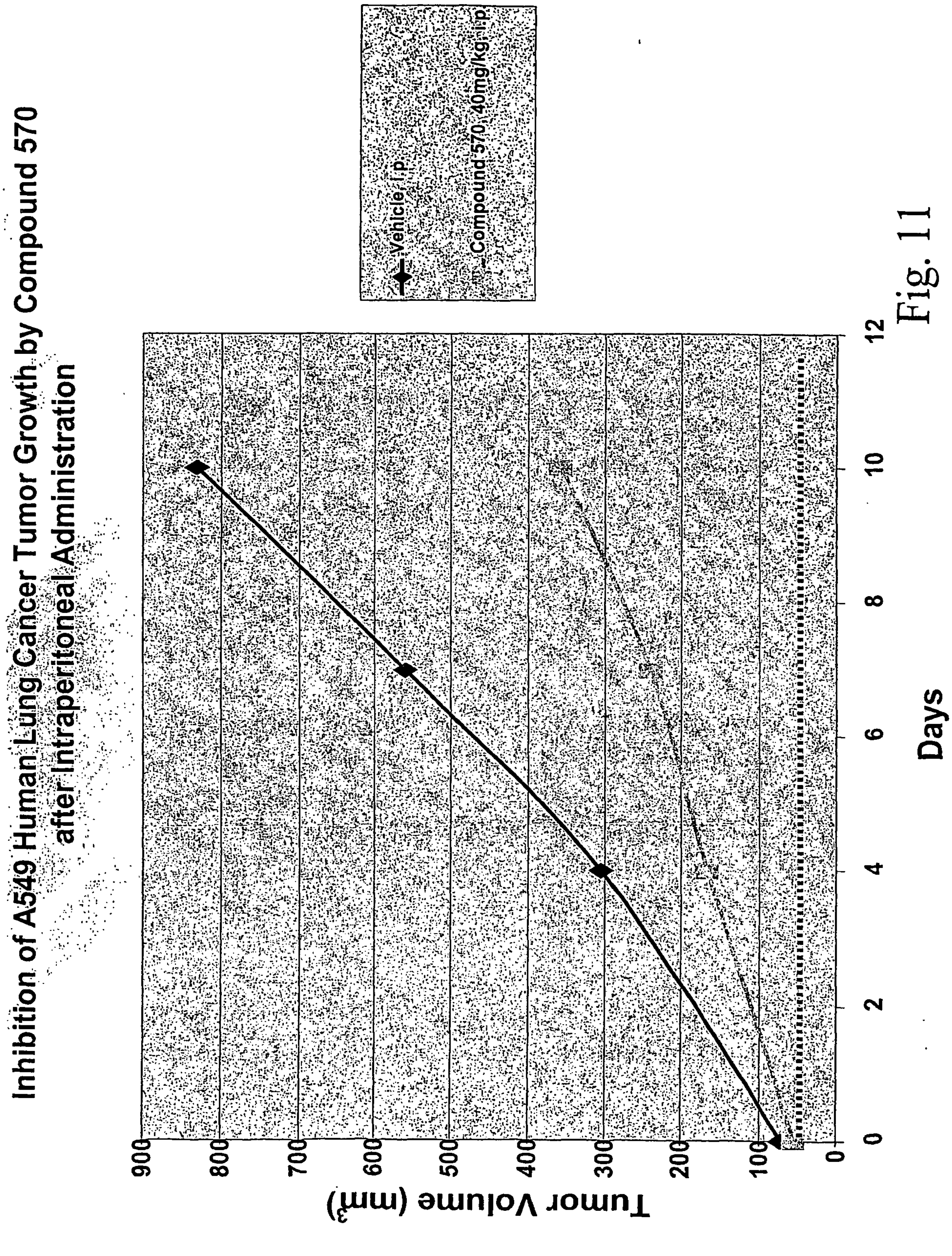

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 570 after Intraperitoneal Administration
Tumor Volume (mm³)
900
800
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
Days
Vehicle, i.p.
Compound 570, 40mg/kg, i.p.

Fig. 11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/000139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 A61K31/506 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 01/38322 A (METHYLGENE INC) 31 May 2001 (2001-05-31) page 11	1-4
Y	EP 0 847 992 A (MITSUI CHEMICALS INC) 17 June 1998 (1998-06-17) claim 1; examples	1-4
P,X	WO 03/024448 A (MORADEL OSCAR ; DELORME DANIEL (CA); LEIT SILVANA (CA); METHYLGENE INC) 27 March 2003 (2003-03-27) page 179; example 433	1-4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2004	19/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA2004/000139

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
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			US	6174905	B1	16-01-2001
WO 03024448	A	27-03-2003	EP	1429765	A2	23-06-2004
			WO	03024448	A2	27-03-2003
			US	2004106599	A1	03-06-2004